09763813

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09  ZDB will be removed from STN
 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 20  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03  JAPIO has been reloaded and enhanced

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)
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09763813

FILE 'HOME' ENTERED AT 16:57:04 ON 03 SEP 2002

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 16:57:10 ON 03 SEP 2002
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STRUCTURE FILE UPDATES: 2 SEP 2002 HIGHEST RN 446017-05-6
DICTIONARY FILE UPDATES: 2 SEP 2002 HIGHEST RN 446017-05-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

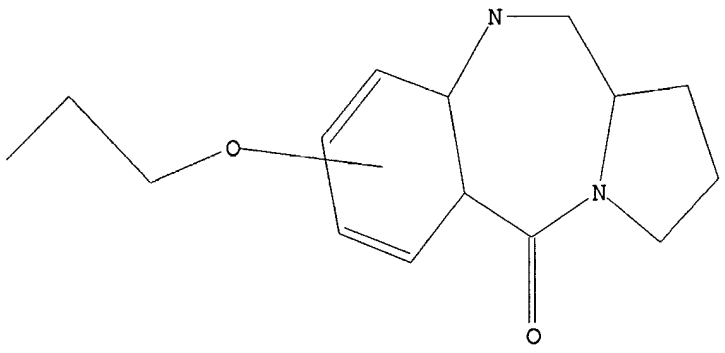
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09763813e.str

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 N

Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss sam

09763813

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SAMPLE SEARCH INITIATED 16:57:54 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    166 TO ITERATE

100.0% PROCESSED     166 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         2547 TO     4093
PROJECTED ANSWERS:               1 TO       80

L2            1 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 16:58:01 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   3424 TO ITERATE

100.0% PROCESSED    3424 ITERATIONS                               82 ANSWERS
SEARCH TIME: 00.00.01

L3           82 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   140.66     140.87

FILE 'CAPLUS' ENTERED AT 16:58:06 ON 03 SEP 2002
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FILE COVERS 1907 - 3 Sep 2002  VOL 137 ISS 10
FILE LAST UPDATED: 2 Sep 2002  (20020902/ED)

  This file contains CAS Registry Numbers for easy and accurate
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CAS roles have been modified effective December 16, 2001. Please
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information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> s l3 full
L4           19 L3

=> d l4 1-19 ibib abs hitstr

L4   ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2002 ACS
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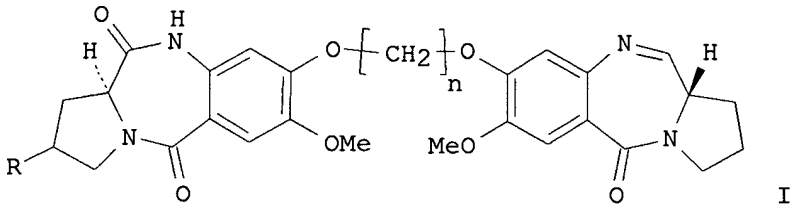
09763813

ACCESSION NUMBER: 2002:237375 CAPLUS
DOCUMENT NUMBER: 136:263030
TITLE: Preparation of pyrrolobenzodiazepines as antitumor agents
INVENTOR(S): Kamal, Ahmed; Nallan, Chakravarthy Laxman; Gujjar, Ramesh; Poddutoori, Ramulu; Olepu, Srinivas
PATENT ASSIGNEE(S): Council of Scientific and Industrial Research, India
SOURCE: U.S., 12 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6362331	B1	20020326	US 2001-822782	20010330

OTHER SOURCE(S): CASREACT 136:263030; MARPAT 136:263030
GI



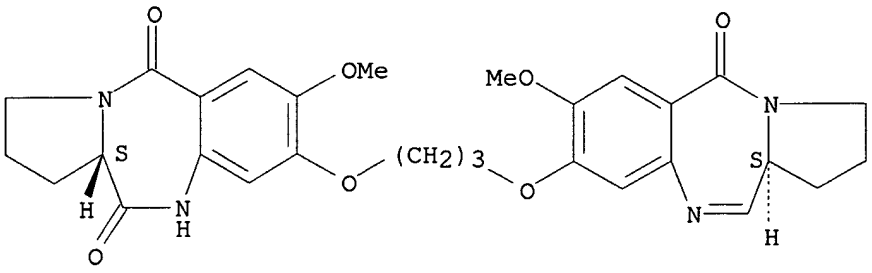
I

AB The present invention provides a process for the prepn. of a novel pyrrolo[2,1-c][1,4]benzodiazepine of formula I [R = H, OH, OAc; n = 3-5], by reacting (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzyl]-pyrrolidine-2-carboxaldehyde di-Et thioacetal with a dibromoalkane, isolating (2S)-N-[4-(3-bromoalkoxy)-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde di-Et thioacetal so formed and reacting the isolate with a dilactam, isolating 8-{[(2S)-N-5-methoxy-2-nitrobenzoyl]pyrrolidin-2-carbaldehyde diethylthioacetal}-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reducing the above nitro compd., isolating the 8-[[(2S)-N-5-methoxy-2-aminobenzoyl]pyrrolidin-2-carbaldehyde diethylthioacetal]-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reacting the amino compd. above with a deprotecting agent to obtain the pyrrolo[2,1-c][1,4]benzodiazepines. The pyrrolo[2,1-c][1,4]benzodiazepines are useful as antitumor agents. Thus, II (R = H, n = 5) was prepd. as described above and showed significant DNA binding affinity and anticancer activity against three human cell lines.

IT **343308-43-0P 343308-44-1P 343308-45-2P**
405108-10-3P 405108-11-4P 405108-12-5P
405108-13-6P 405108-14-7P 405108-15-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrolobenzodiazepines as antitumor agents)

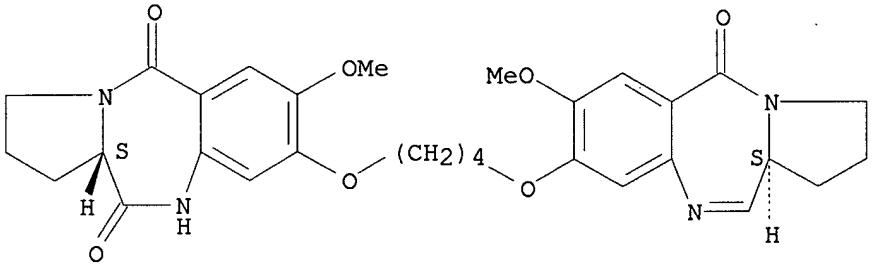
RN 343308-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



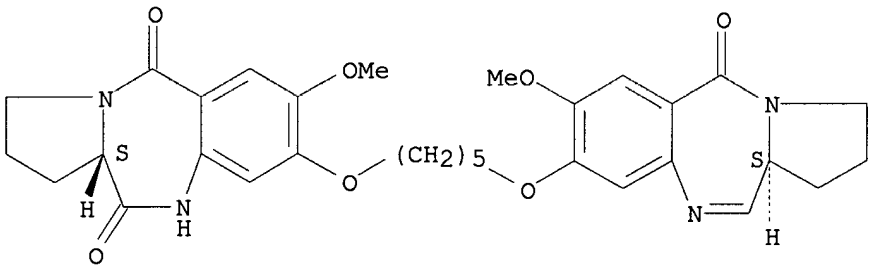
RN 343308-44-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



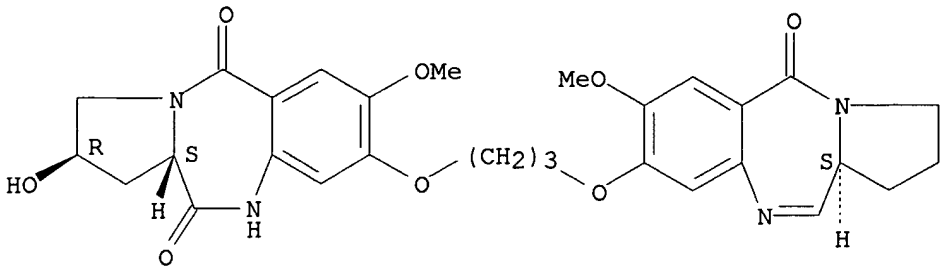
RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



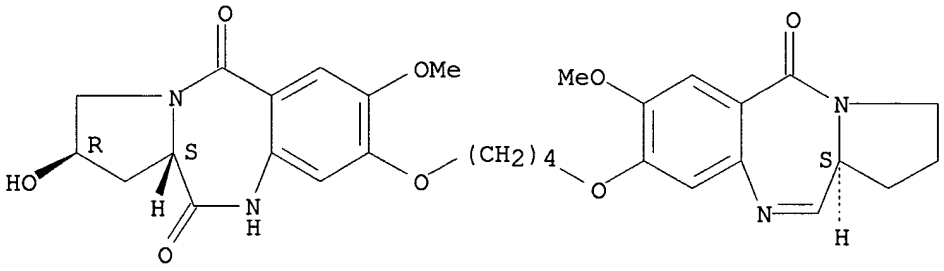
RN 405108-10-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



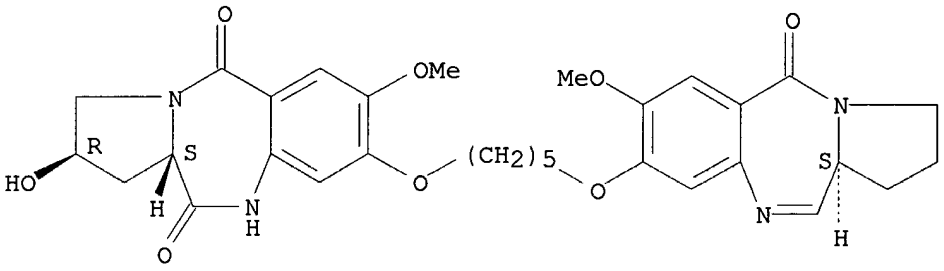
RN 405108-11-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



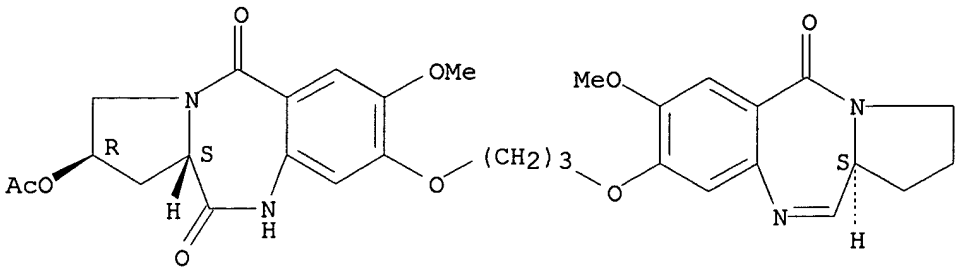
RN 405108-12-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



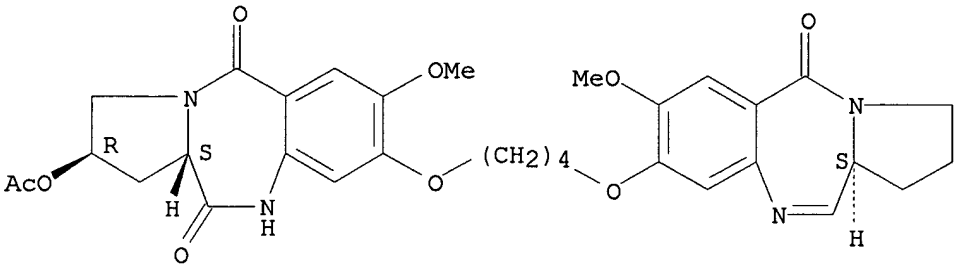
RN 405108-13-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



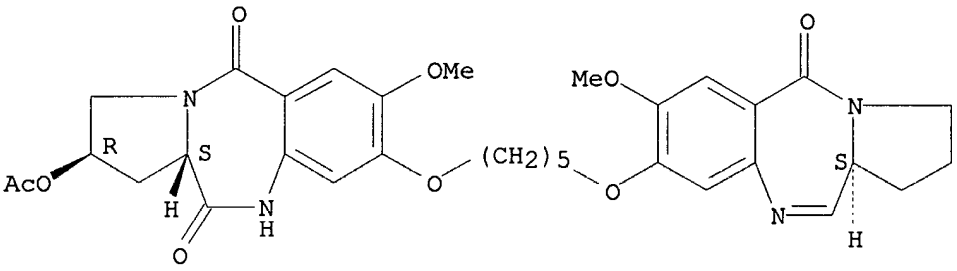
RN 405108-14-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 405108-15-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

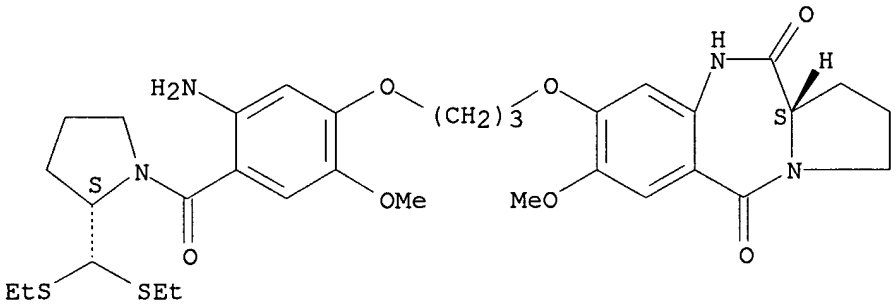


IT **343308-61-2P 343308-62-3P 343308-63-4P**
405108-16-9P 405108-17-0P 405108-18-1P
405108-20-5P 405108-22-7P 405108-24-9P
405108-26-1P 405108-27-2P 405108-31-8P
405108-34-1P 405108-35-2P 405108-36-3P
405108-37-4P 405108-38-5P 405108-39-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrolobenzodiazepines as antitumor agents)

RN 343308-61-2 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[3-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-

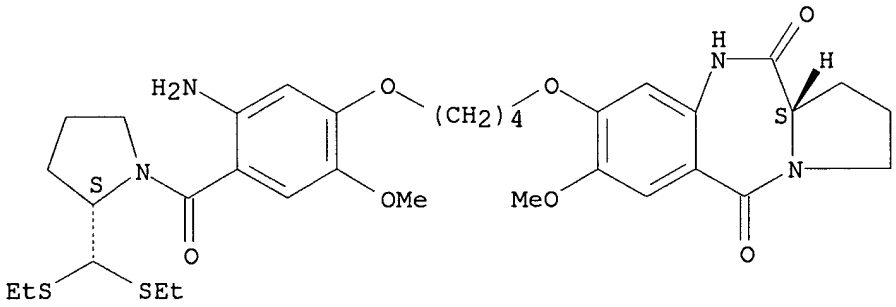
5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



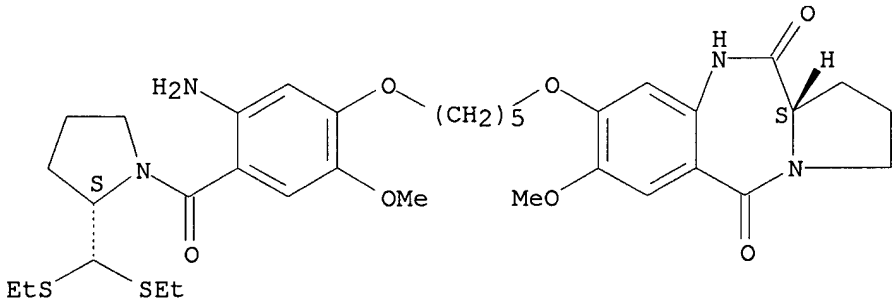
RN 343308-62-3 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[4-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 343308-63-4 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[[5-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

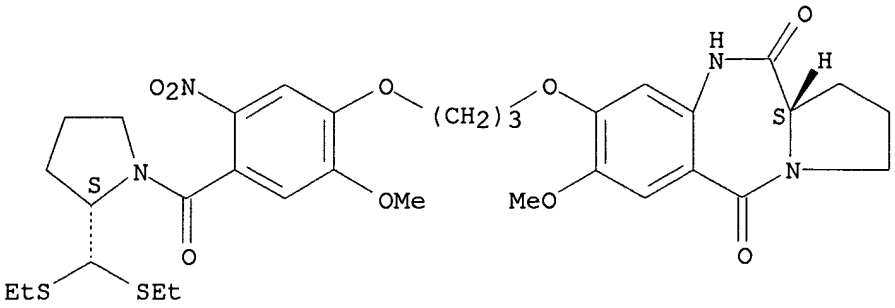
Absolute stereochemistry.



RN 405108-16-9 CAPLUS
CN Pyrrolidine, 2-[bis(ethylthio)methyl]-1-[4-[3-[[(11aS)-2,3,5,10,11,11a-

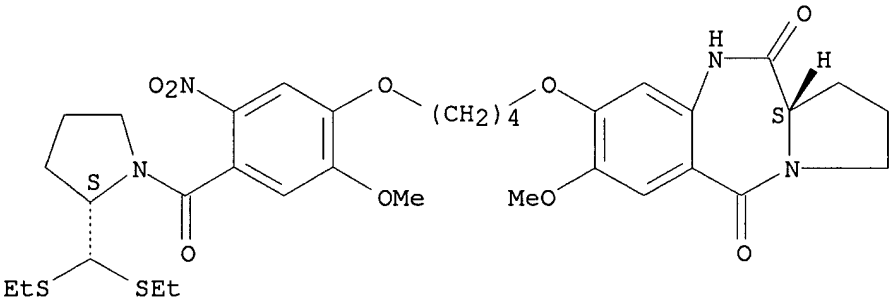
hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-5-methoxy-2-nitrobenzoyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



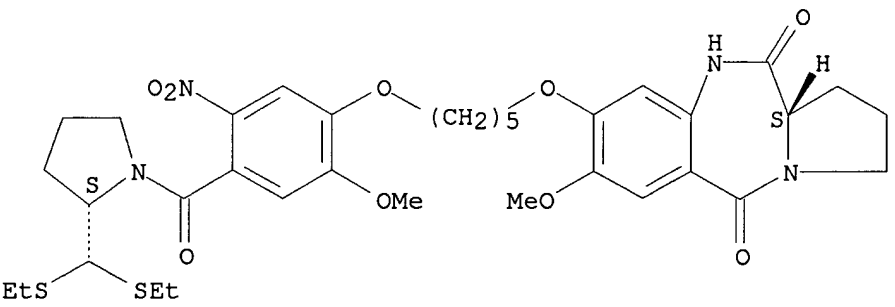
RN 405108-17-0 CAPLUS
CN Pyrrolidine, 2-[bis(ethylthio)methyl]-1-[4-[4-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-5-methoxy-2-nitrobenzoyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 405108-18-1 CAPLUS
CN Pyrrolidine, 2-[bis(ethylthio)methyl]-1-[4-[[5-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-5-methoxy-2-nitrobenzoyl]-, (2S)- (9CI) (CA INDEX NAME)

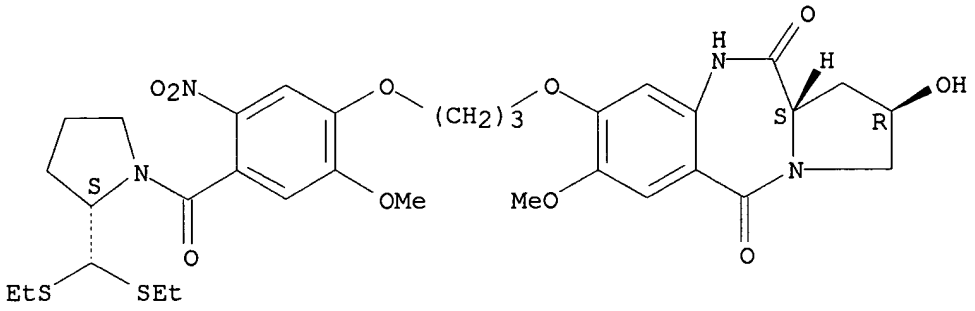
Absolute stereochemistry.



RN 405108-20-5 CAPLUS

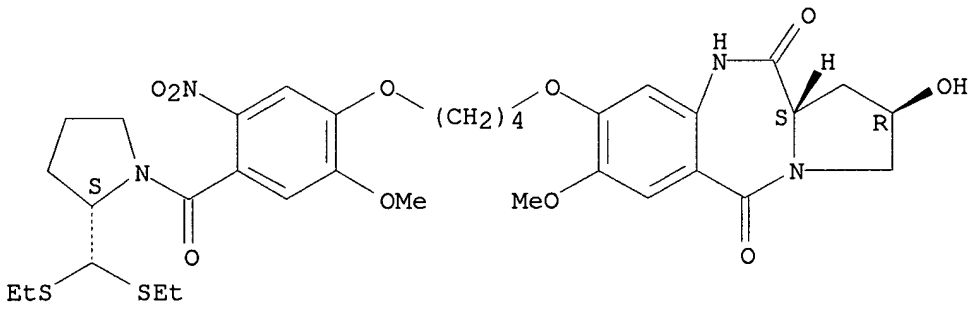
CN Pyrrolidine, 2-[bis(ethylthio)methyl]-1-[4-[3-[[(2R,11aS)-2,3,5,10,11,11a-hexahydro-2-hydroxy-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-5-methoxy-2-nitrobenzoyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



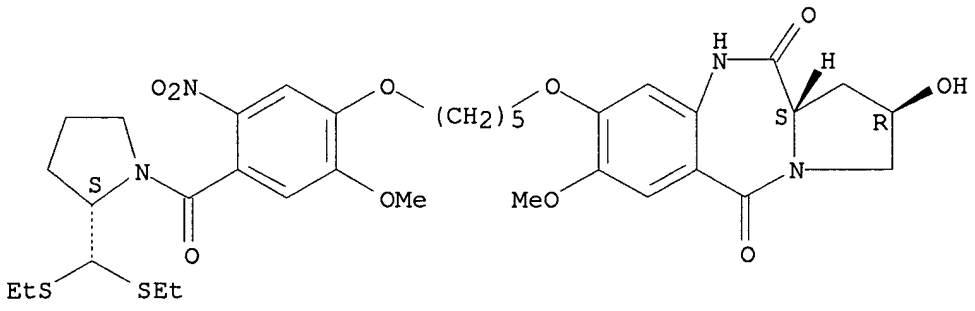
RN 405108-22-7 CAPLUS
CN Pyrrolidine, 2-[bis(ethylthio)methyl]-1-[4-[4-[[(2R,11aS)-2,3,5,10,11,11a-hexahydro-2-hydroxy-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-5-methoxy-2-nitrobenzoyl]-, (2S)- (9CI) (CA INDEX NAME)

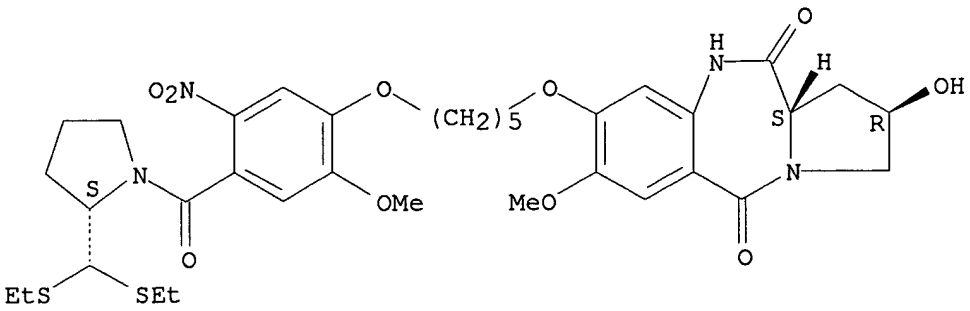
Absolute stereochemistry.



RN 405108-24-9 CAPLUS
CN Pyrrolidine, 2-[bis(ethylthio)methyl]-1-[4-[[5-[[(2R,11aS)-2,3,5,10,11,11a-hexahydro-2-hydroxy-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-5-methoxy-2-nitrobenzoyl]-, (2S)- (9CI) (CA INDEX NAME)

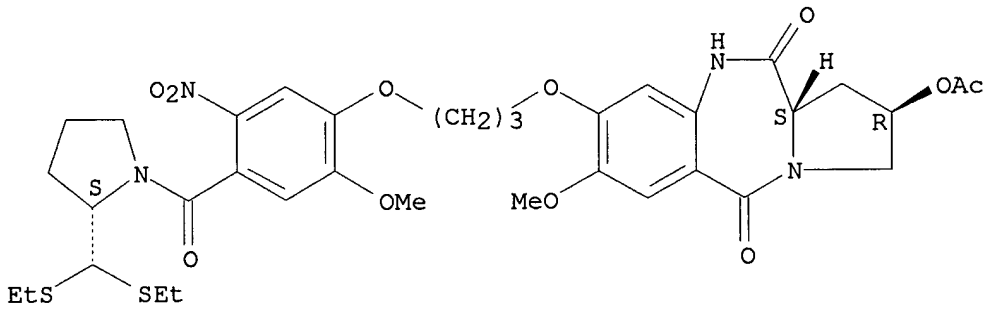
Absolute stereochemistry.





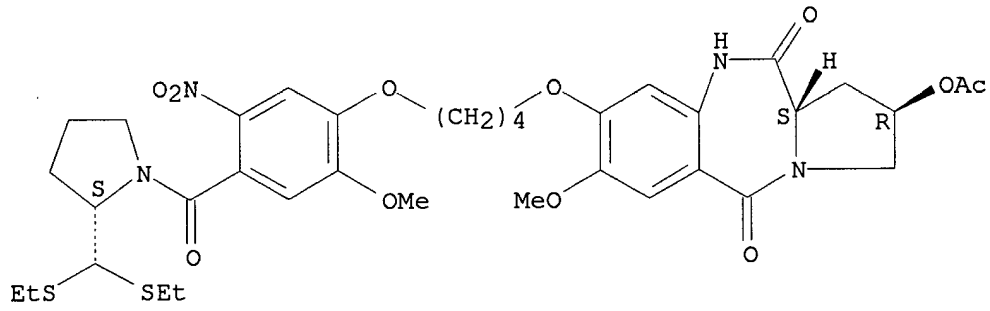
RN 405108-26-1 CAPLUS
CN Pyrrolidine, 1-[4-[3-[[(2R,11aS)-2-(acetyloxy)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-5-methoxy-2-nitrobenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



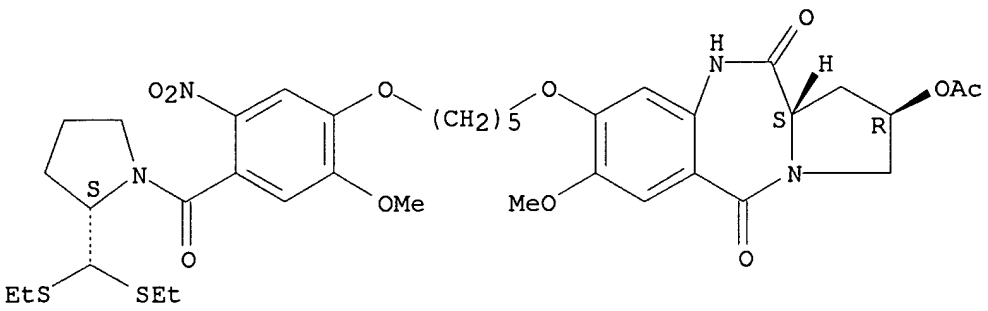
RN 405108-27-2 CAPLUS
CN Pyrrolidine, 1-[4-[4-[[(2R,11aS)-2-(acetyloxy)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-5-methoxy-2-nitrobenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



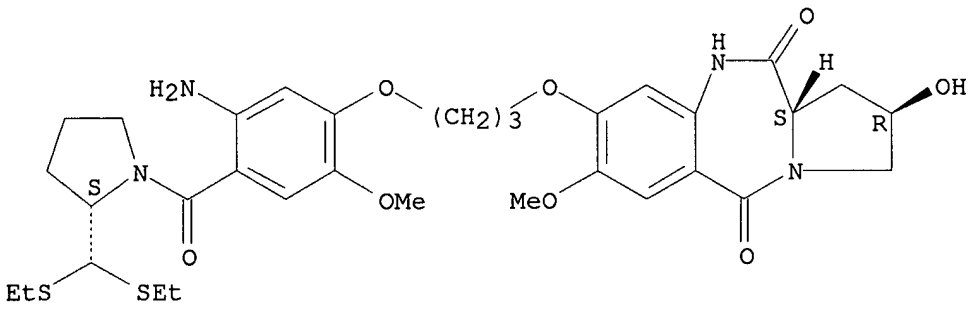
RN 405108-31-8 CAPLUS
CN Pyrrolidine, 1-[4-[[5-[[(2R,11aS)-2-(acetyloxy)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-5-methoxy-2-nitrobenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



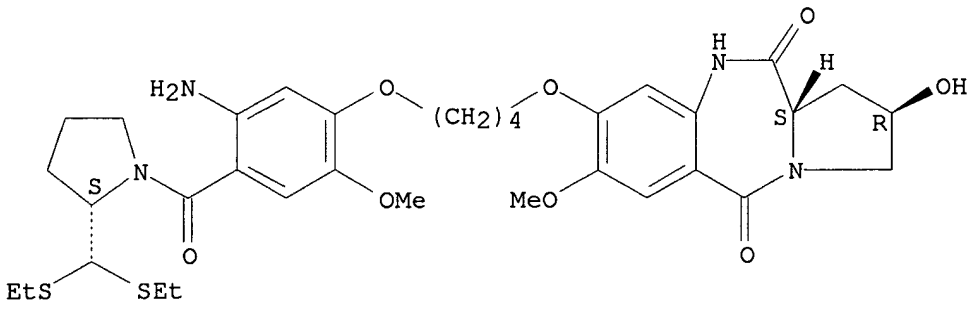
RN 405108-34-1 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[3-[[(2R,11aS)-2,3,5,10,11,11a-hexahydro-2-hydroxy-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 405108-35-2 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[4-[[(2R,11aS)-2,3,5,10,11,11a-hexahydro-2-hydroxy-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

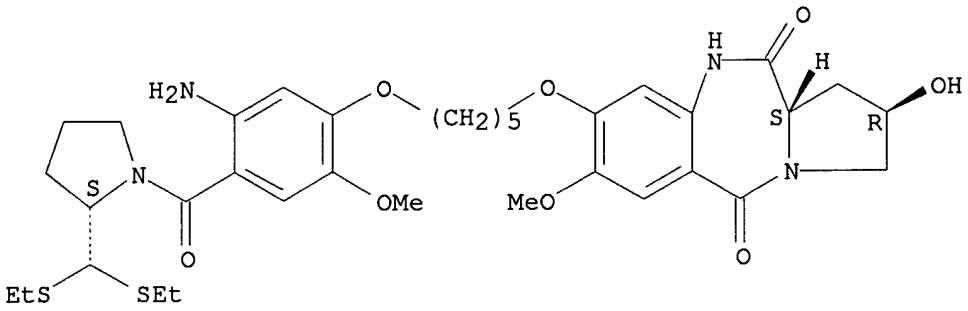
Absolute stereochemistry.



RN 405108-36-3 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[[5-[[(2R,11aS)-2,3,5,10,11,11a-hexahydro-2-

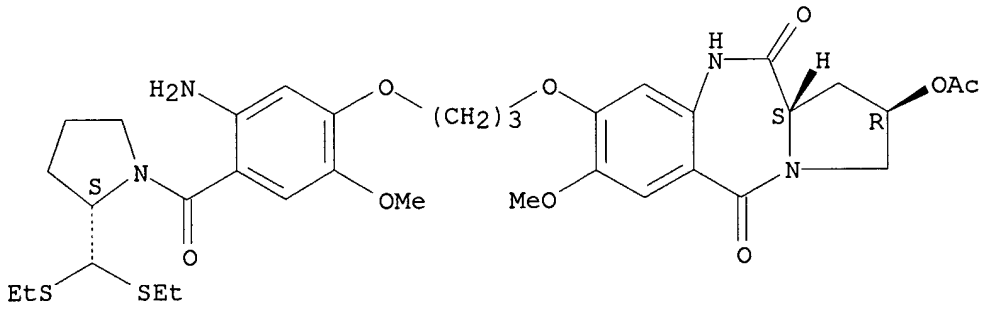
hydroxy-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



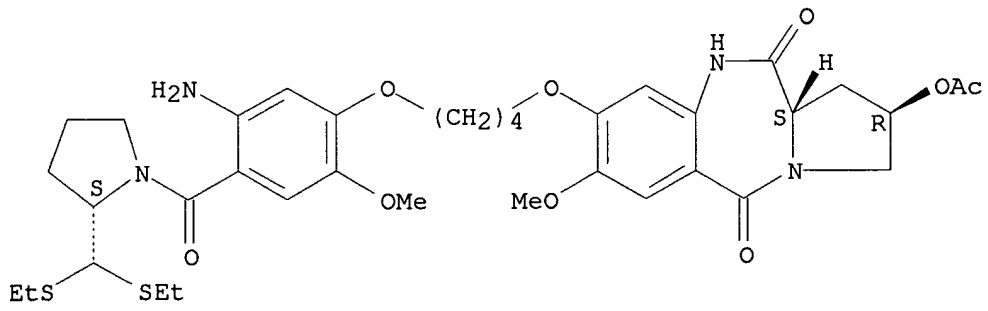
RN 405108-37-4 CAPLUS
CN Pyrrolidine, 1-[4-[3-[[(2R,11aS)-2-(acetyloxy)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-2-amino-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 405108-38-5 CAPLUS
CN Pyrrolidine, 1-[4-[4-[[(2R,11aS)-2-(acetyloxy)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-2-amino-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

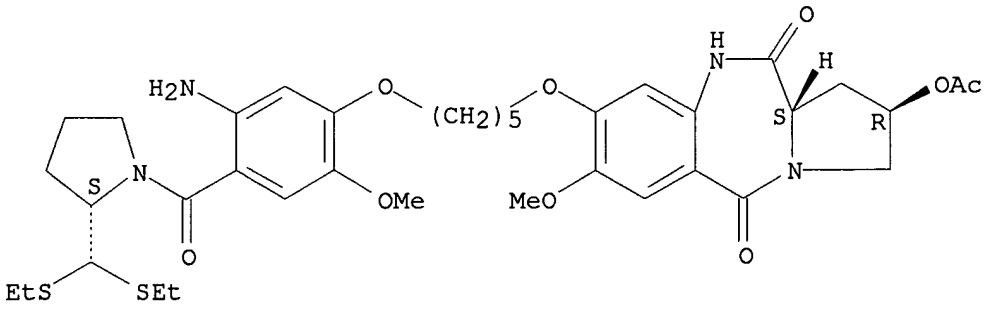
Absolute stereochemistry.



09763813

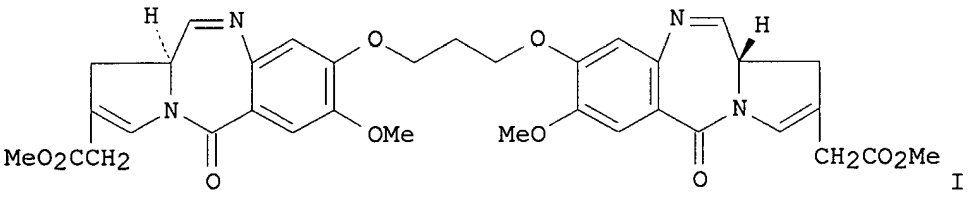
RN 405108-39-6 CAPLUS
CN Pyrrolidine, 1-[4-[[5-[[(2R,11aS)-2-(acetyloxy)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-2-amino-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

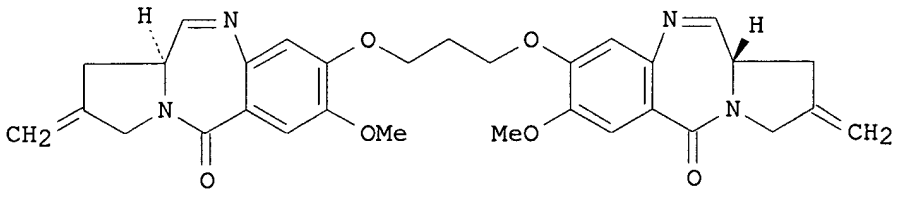


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:746612 CAPLUS
DOCUMENT NUMBER: 136:200170
TITLE: Synthesis of the first example of a C2-C3/C2'-C3'-endo unsaturated pyrrolo[2,1-c][1,4]benzodiazepine dimer
AUTHOR(S): Gregson, S. J.; Howard, P. W.; Corcoran, K. E.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E.
CORPORATE SOURCE: Cancer Research Laboratories, CRC Gene Targeted Drug Design Research Group, University of Nottingham, School of Pharmaceutical Sciences, Nottingham, NG7 2RD, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(21), 2859-2862
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

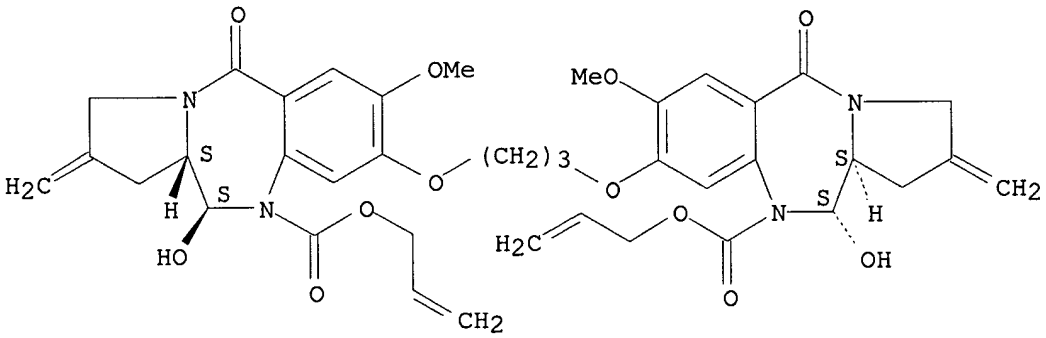
AB We report the first example of a C2-C3/C2'-C3'-endo unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer (I) synthesized through a new and efficient route, thus establishing that C2-C3-endo unsatn. enhances both cytotoxicity and DNA-binding affinity in A-ring-linked PBD dimers but to a lesser extent than C2/C2'-exo-unsatn. This new route has allowed the prepn. of multigram quantities of the related clin. candidate II and should lead to more structurally diverse PBD dimer analogs.

IT **232931-64-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of first example of C2-C3/C2'-C3'-endo unsatd. pyrrolo[2,1-c][1,4]benzodiazepine dimer)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:304925 CAPLUS

DOCUMENT NUMBER: 135:107180

TITLE: Design and Synthesis of a Novel DNA-DNA Interstrand Adenine-Guanine Cross-Linking Agent

AUTHOR(S): Zhou, Qun; Duan, Wenhu; Simmons, Denise; Shayo, Yuda; Raymond, Mary Ann; Dorr, Robert T.; Hurley, Laurence H.

CORPORATE SOURCE: Arizona Cancer Center, Tucson, AZ, 85724, USA

SOURCE: Journal of the American Chemical Society (2001), 123(20), 4865-4866
CODEN: JACSAT; ISSN: 0002-7863

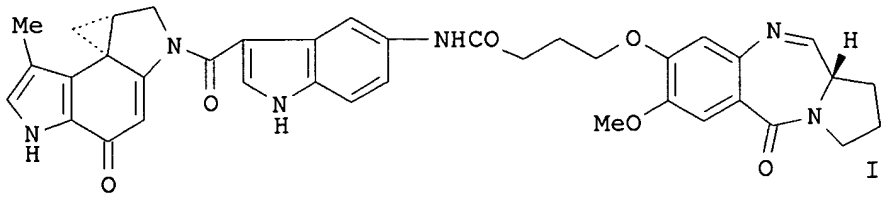
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 135:107180

GI

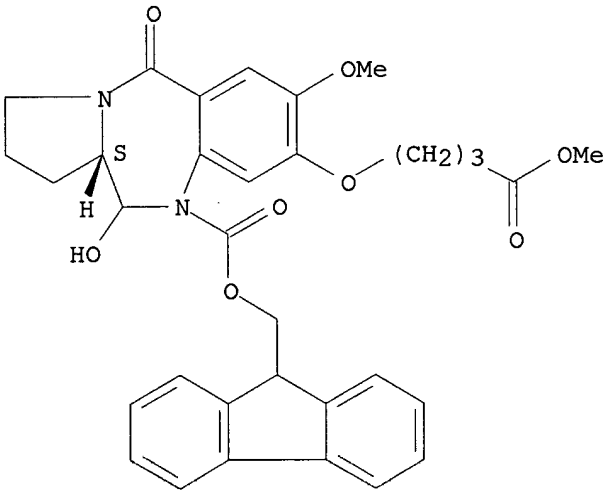


AB The heterobifunctional compd. UTA-6026 (I) that forms interstrand cross linking between adenine and guanine six base pairs apart was designed and synthesized in 10 steps starting from vanillic acid in 6% overall yield. It shows mixed sequence-specific alkylation selectivity and demonstrates potent antitumor activity against several tumor cell lines.

IT **349536-28-3P 349536-29-4P 349536-30-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design and synthesis of a novel DNA-DNA interstrand adenine-guanine crosslinking agent)

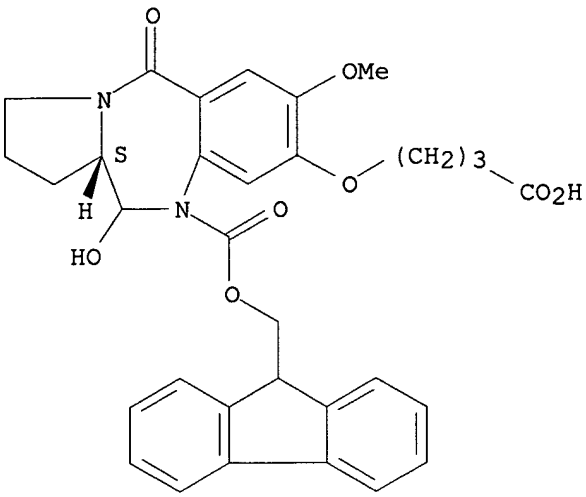
RN 349536-28-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-, 9H-fluoren-9-ylmethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 349536-29-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(9H-fluoren-9-ylmethyl) ester, (11aS)- (9CI) (CA INDEX NAME)

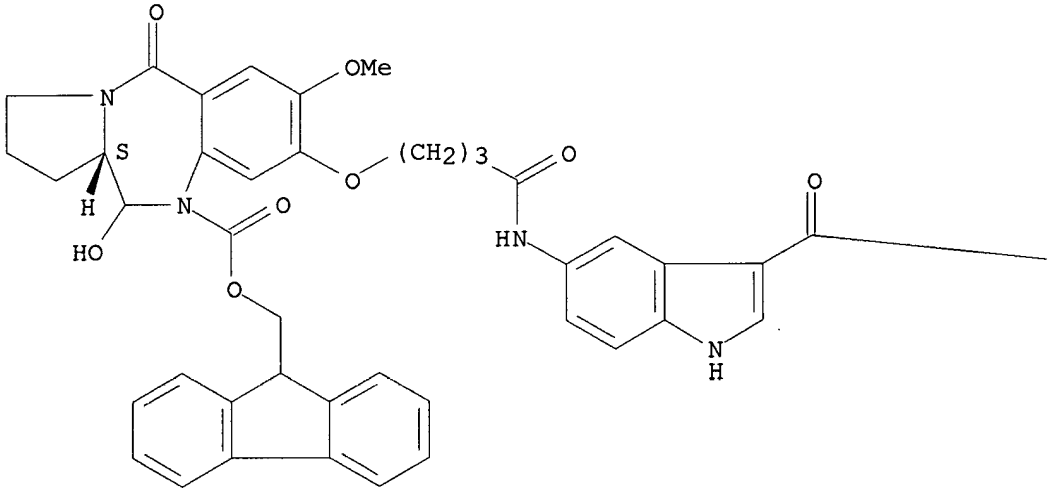
Absolute stereochemistry.

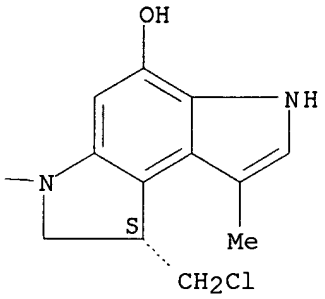


RN 349536-30-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[4-[[3-[[(1S)-1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 9H-fluoren-9-ylmethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

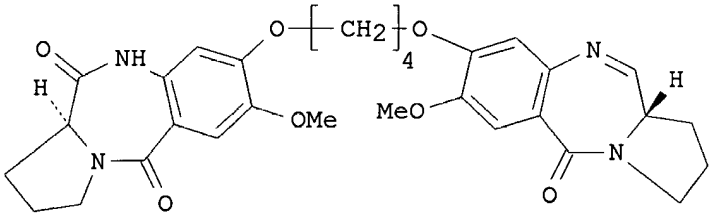
PAGE 1-A





REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:139435 CAPLUS
DOCUMENT NUMBER: 135:13847
TITLE: Synthesis of novel non-cross-linking pyrrolobenzodiazepines with remarkable DNA binding affinity and potent antitumour activity
AUTHOR(S): Kamal, Ahmed; Laxman, N.; Ramesh, G.; Neelima, K.; Kondapi, Anand K.
CORPORATE SOURCE: Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SOURCE: Chemical Communications (Cambridge, United Kingdom) (2001), (5), 437-438
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:13847
GI



I

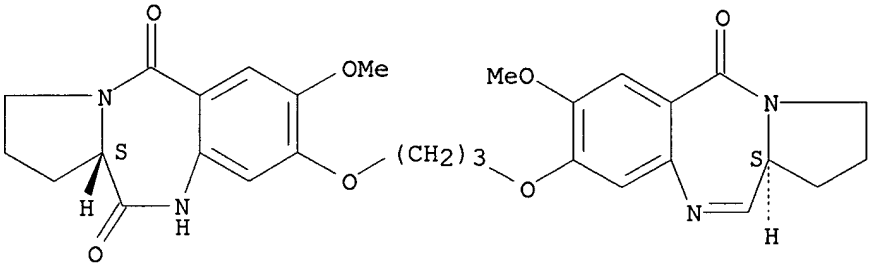
AB Mixed imine-amide pyrrolobenzodiazepine dimers have been prepd. which exhibit potent antitumor activity and have significant DNA binding affinity; one of them, I, has been shown to cause a remarkable rise in the melting temp. of calf thymus DNA.

IT **343308-43-0P 343308-44-1P 343308-45-2P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(pyrrolobenzodiazepines with DNA binding affinity and antitumor activity)

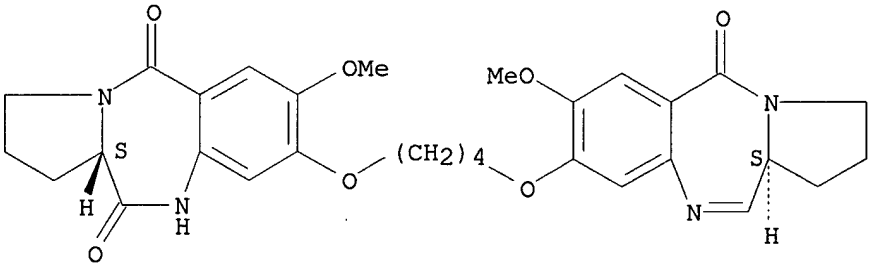
RN 343308-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



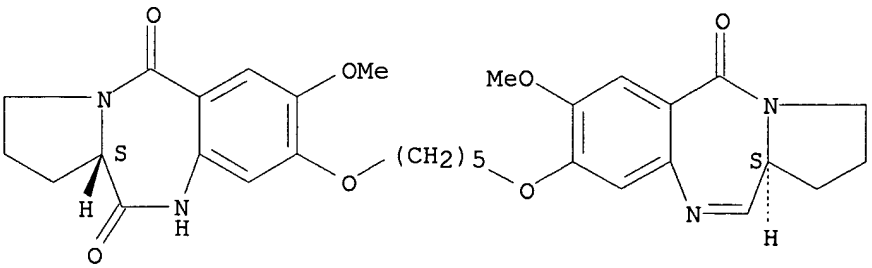
RN 343308-44-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (9CI) (CA INDEX NAME)

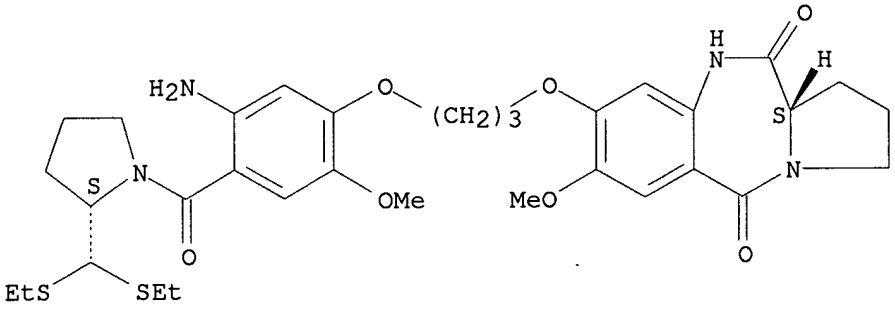
Absolute stereochemistry.



IT **343308-61-2P 343308-62-3P 343308-63-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pyrrolobenzodiazepines with DNA binding affinity and antitumor activity)

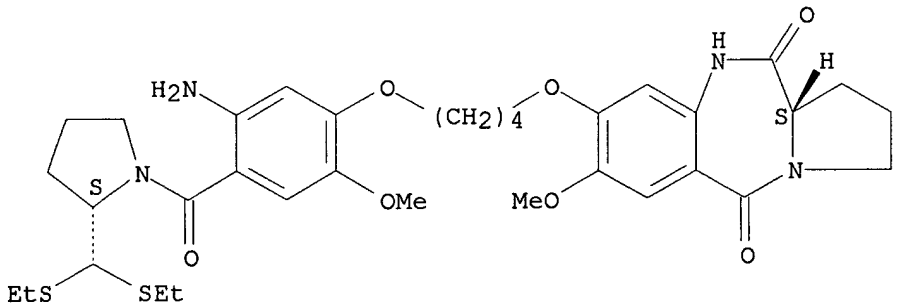
RN 343308-61-2 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[3-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



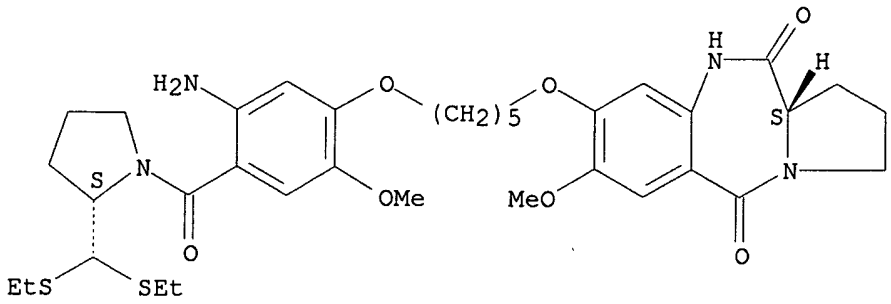
RN 343308-62-3 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[4-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 343308-63-4 CAPLUS
CN Pyrrolidine, 1-[2-amino-4-[[5-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-5-methoxybenzoyl]-2-[bis(ethylthio)methyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

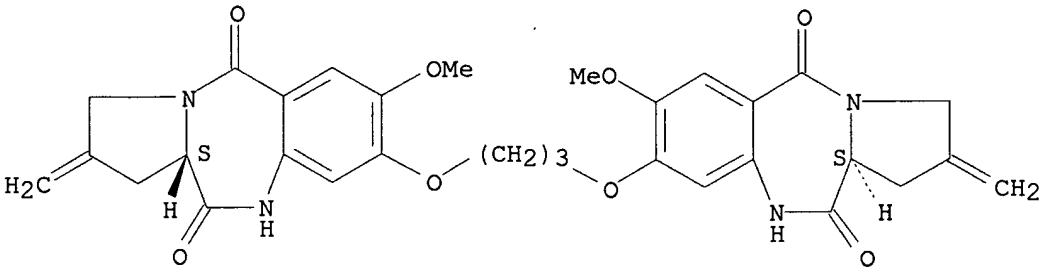
L4 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:68712 CAPLUS
DOCUMENT NUMBER: 134:260871
TITLE: Design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient cross-linking ability and potent cytotoxicity
AUTHOR(S): Gregson, Stephen J.; Howard, Philip W.; Hartley, John A.; Brooks, Natalie A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston, David E.
CORPORATE SOURCE: CRC Gene Targeted Drug Design Research Group, Cancer Research Laboratories University of Nottingham, Nottingham, NG7 2RD, UK
SOURCE: Journal of Medicinal Chemistry (2001), 44(5), 737-748
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:260871

AB A novel sequence-selective pyrrolobenzodiazepine (PBD) dimer 5 (SJG-136) has been developed that comprises two C2-exo-methylene-substituted DC-81 (3) subunits tethered through their C8 positions via an inert propanedioxy linker. This sym. mol. is a highly efficient minor groove interstrand DNA crosslinking agent (XL50 = 0.045 .mu.M) that is 440-fold more potent than melphalan. Thermal denaturation studies show that, after 18 h incubation with calf thymus DNA at a 5:1 DNA/ligand ratio, it increases the Tm value by 33.6.degree., the highest value so far recorded in this assay. The analogous dimer 4 (DSB-120) that lacks substitution/unsatn. at the C2 position elevates melting by only 15.1.degree. under the same conditions, illustrating the effect of introducing C2-exo-unsatn. which serves to flatten the C-rings and achieve a superior isohelical fit within the DNA minor groove. This behavior is supported by mol. modeling studies which indicate that (i) the PBD units are covalently bonded to guanines on opposite strands to form a cross-link, (ii) 5 has a greater binding energy compared to 4, and (iii) 4 and 5 have equiv. binding sites that span six base pairs. Dimer 5 is significantly more cytotoxic than 4 in a no. of human ovarian cancer cell lines (e.g., IC50 values of 0.0225 nM vs. 7.2 nM, resp., in A2780 cells). Furthermore, it retains full potency in the cisplatin-resistant cell line A2780cisR (0.024 nM), whereas 4 loses activity (0.21 .mu.M) with a resistance factor of 29.2. This may be due to a lower level of inactivation of 5 by intracellular thiol-contg. mols. A dilactam analog, tetralactam of 5 that lacks the electrophilic N10-C11/N10'-C11' imine moieties has also been synthesized and evaluated. Although unable to interact covalently with DNA, tetralactam still

stabilizes the helix (.DELTA.Tm = 0.78.degree.) and has significant cytotoxicity in some cell lines (i.e., IC50 = 0.57 .mu.M in CH1 cells), presumably exerting its effect through noncovalent interaction with DNA.

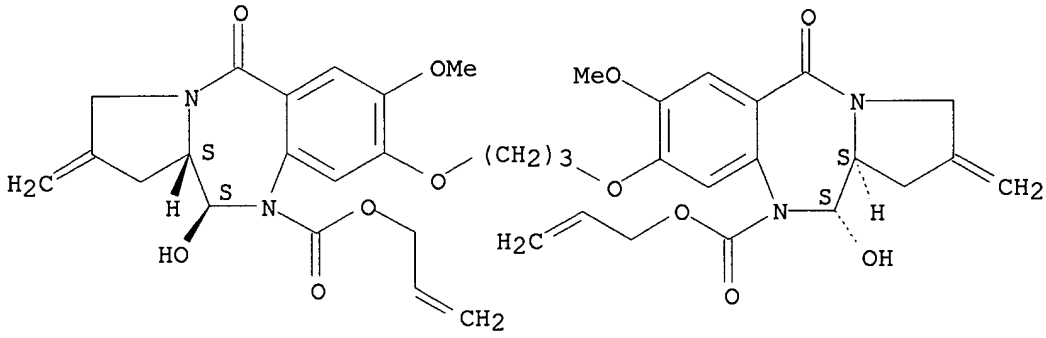
IT **232931-67-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient crosslinking ability and potent cytotoxicity)
RN 232931-67-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT **232931-64-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient crosslinking ability and potent cytotoxicity)
RN 232931-64-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

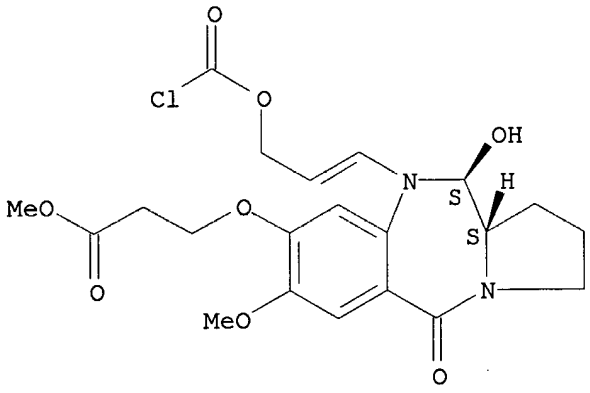
L4 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:787600 CAPLUS
DOCUMENT NUMBER: 134:95090
TITLE: Pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid inhibits DNA binding to transcription factor Sp1
AUTHOR(S): Baraldi, P. G.; Cacciari, B.; Guiotto, A.; Romagnoli, R.; Spalluto, G.; Leoni, A.; Bianchi, N.; Feriotto, G.; Rutigliano, C.; Mischiati, C.; Gambari, Roberto
CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche, Universita di Ferrara, Ferrara, 44100, Italy
SOURCE: Nucleosides, Nucleotides & Nucleic Acids (2000), 19(8), 1219-1229
CODEN: NNNAFY; ISSN: 1525-7770
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The hybrid was designed and synthesized,which was prepd. combining the minor groove binders distamycin A and pyrrolo[2,1-c][1,4]benzodiazepine (PBD) 4, related to the natural occurring anthramycin and DC-81. The effects of the hybrid on mol. interactions between DNA and transcription factor Sp1 were studied. Thus, PBD-distamycin hybrid is a powerful inhibitor of Sp1/DNA interactions.

IT **319477-08-2P 319477-11-7P 319477-13-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pyrrolo[2,1-c][1,4]benzodiazepine-distamycin hybrid inhibits DNA binding to transcription factor Sp1)

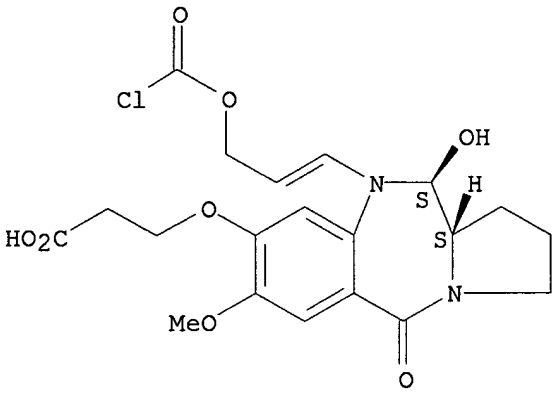
RN 319477-08-2 CAPLUS
CN Propanoic acid, 3-[[(11S,11aS)-10-[3-[(chlorocarbonyl)oxy]-1-propenyl]-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 319477-11-7 CAPLUS
CN Propanoic acid, 3-[[(11S,11aS)-10-[3-[(chlorocarbonyl)oxy]-1-propenyl]-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (9CI) (CA INDEX NAME)

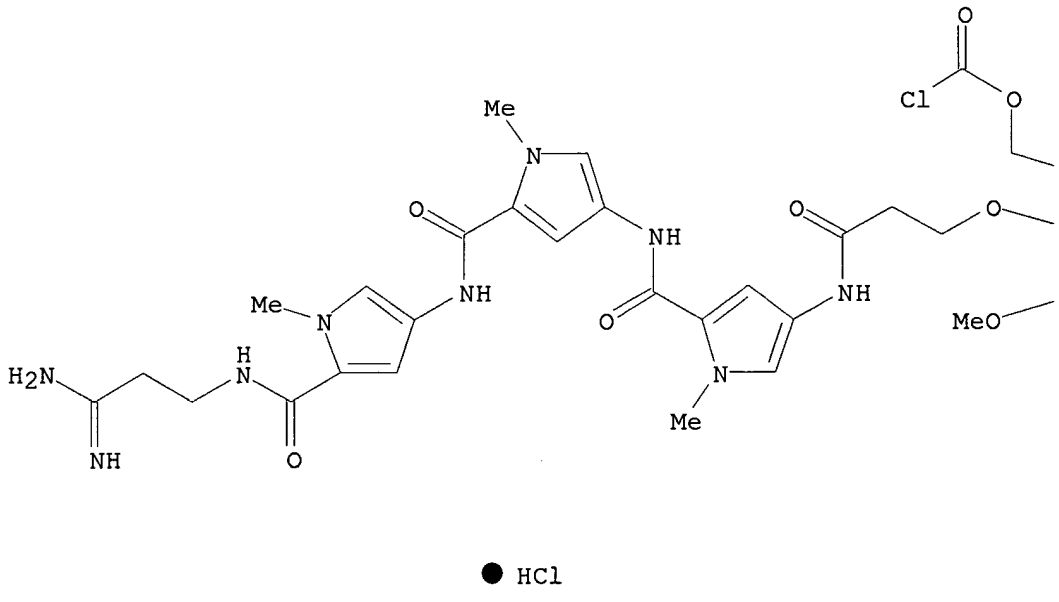
Absolute stereochemistry.
Double bond geometry unknown.



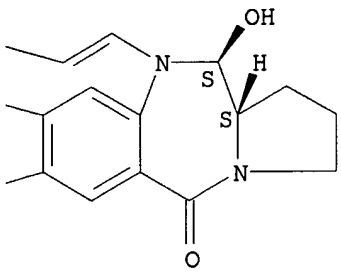
RN 319477-13-9 CAPLUS
CN Carbonochloridic acid, 3-[(11S,11aS)-8-[3-[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]-2-propenyl ester, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



● HCl



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

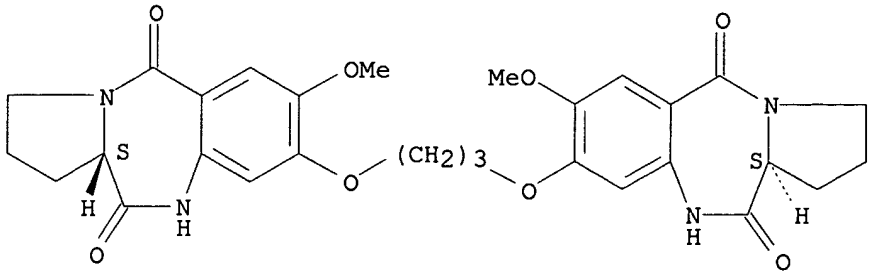
L4 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:719703 CAPLUS
DOCUMENT NUMBER: 134:56501
TITLE: Synthesis of pyrrolo[2,1-c][1,4]benzodiazepines via reductive cyclization of .omega.-azido carbonyl compounds by TMSI: an efficient preparation of antibiotic DC-81 and its dimers
AUTHOR(S): Kamal, A.; Laxman, E.; Laxman, N.; Venugopal Rao, N.
CORPORATE SOURCE: Division of Organic Chemistry-I, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(20), 2311-2313
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:56501

AB .omega.-Azido carbonyl compds. on reaction with trimethylsilyl iodide (in situ prepd. from TMSCl/NaI) led to the formation of diazepine imines in good yields under mild conditions. This methodol. has been applied to the parent unsubstituted pyrrolobenzodiazepine, the natural product DC-81 and its dimers.

IT **313644-35-8P 313644-44-9P 313644-45-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(efficient synthesis of antibiotic DC-81 and its dimers via reductive cyclization of .omega.-azido carbonyl compds. by TMSI)

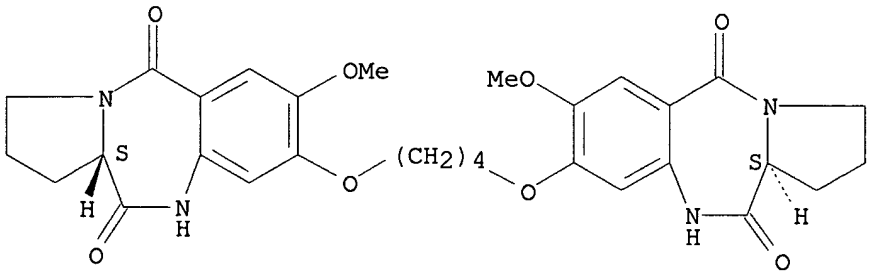
RN 313644-35-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



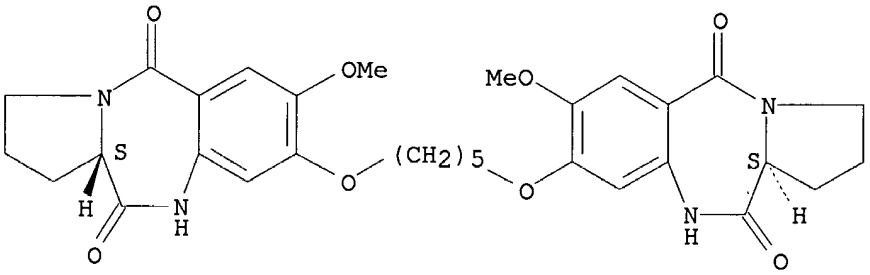
RN 313644-44-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,4-butanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313644-45-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:619247 CAPLUS
DOCUMENT NUMBER: 133:362758
TITLE: Design and synthesis of novel pyrrolobenzodiazepine (PBD) prodrugs for ADEPT and GDEPT
AUTHOR(S): Sagnou, M. J.; Howard, P. W.; Gregson, S. J.; Eno-Amooquaye, E.; Burke, P. J.; Thurston, D. E.

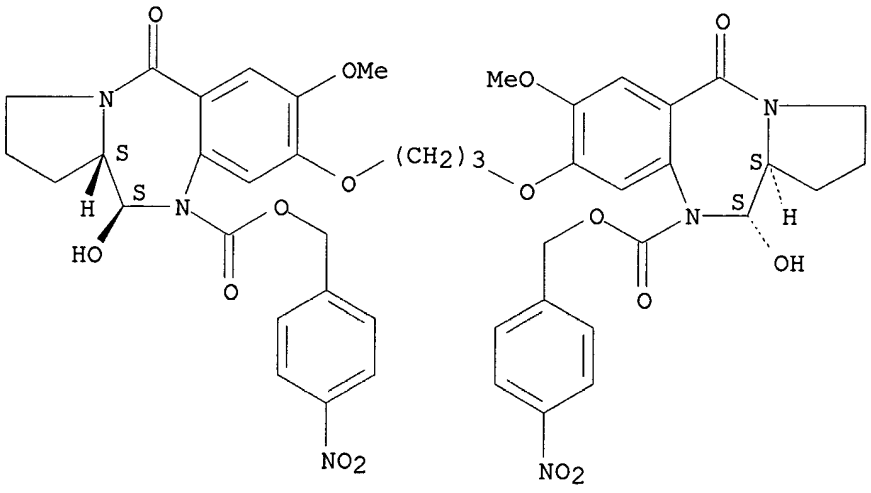
09763813

CORPORATE SOURCE: School of Pharmacy and Biomedical Sciences, CRC Gene Targeting Drug Design Research Group, University of Portsmouth, Hants, PO1 2DT, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(18), 2083-2086
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:362758

AB Three N10-(4-nitrobenzyl)carbamate-protected PBD prodrugs were prepd. and evaluated for potential use in nitro reductase-based ADEPT (antibody-directed enzyme chemotherapy) and GDEPT (gene-directed chemotherapy). For example, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid (4-nitrophenyl)methyl ester was prepd., which is a prodrug precursor to benzyl DC 81. An approx. 100-fold activation was obsd. for benzyl DC 81.

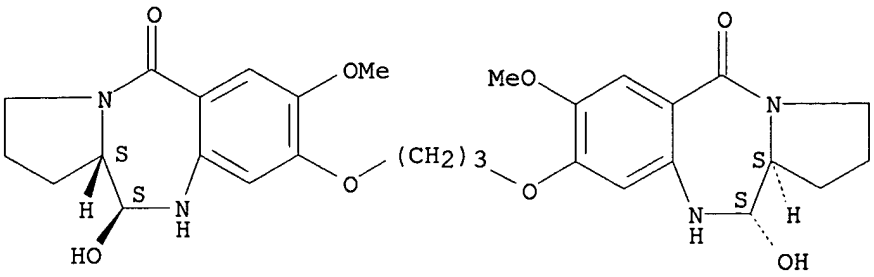
IT **307925-16-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))
RN 307925-16-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **307925-17-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))
RN 307925-17-3 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:244166 CAPLUS
DOCUMENT NUMBER: 133:4639
TITLE: Synthesis of polyaminoalkyl substituted conjugates of pyrrolo[2,1-c][1,4]benzodiazepine involving SNAr reaction of 2-nitro-5-fluorobenzoate precursors
AUTHOR(S): Matsumoto, Kiyoshi; Iida, Hirokazu; Lown, J. William
CORPORATE SOURCE: Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, 606-8501, Japan
SOURCE: Heterocycles (2000), 52(3), 1015-1020
CODEN: HTCYAM; ISSN: 0385-5414
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

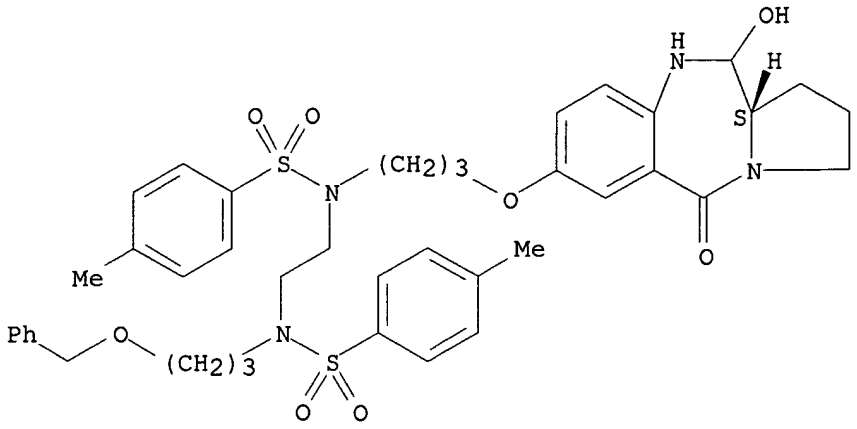
AB A synthetic procedure is described for conjugating polyaminoalkyl groups to the pyrrolo[2,1-c][1,4]benzodiazepine pharmacophore in order to alter its characteristic DNA sequence binding preference. To this end SNAr reactions of 2-nitro-5-fluorobenzoate esters with different polyaminoalkyl side chains were examd. and incorporated in the synthetic scheme.

IT **271253-13-5P 271253-15-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of polyaminoalkyl-substituted pyrrolo[2,1-c][1,4]benzodiazepines)

RN 271253-13-5 CAPLUS
CN Benzenesulfonamide, N-[3-[[(11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-7-yl]oxy]propyl]-4-methyl-N-[2-[[(4-methylphenyl)sulfonyl][3-(phenylmethoxy)propyl]amino]ethyl]- (9CI) (CA INDEX NAME)

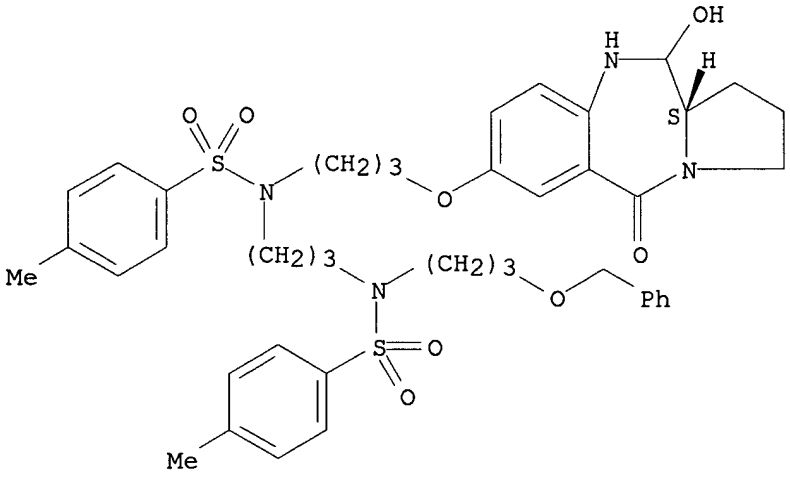
Absolute stereochemistry.

09763813



RN 271253-15-7 CAPLUS
CN Benzenesulfonamide, N-[3-[[(11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-7-yl]oxy]propyl]-4-methyl-N-[3-[[(4-methylphenyl)sulfonyl][3-(phenylmethoxy)propyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:161285 CAPLUS
DOCUMENT NUMBER: 132:207852
TITLE: Solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivatives for drug screening
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012509	A2	20000309	WO 1999-GB2839	19990827
WO 2000012509	A3	20000706		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9955262	A1	20000321	AU 1999-55262	19990827
EP 1107970	A2	20010620	EP 1999-941767	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525286	T2	20020813	JP 2000-571055	19990827

PRIORITY APPLN. INFO.: GB 1998-18732 A 19980827
WO 1999-GB2839 W 19990827

OTHER SOURCE(S): MARPAT 132:207852
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

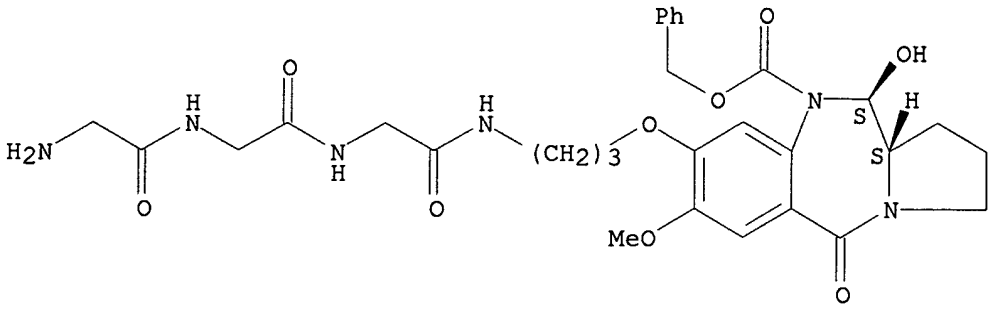
AB Title compds. I are prepd. [wherein: R = (un)substituted alk(en/yn)yl, aralkyl, aryl, or heteroat. analogs; R2 and R3 = H, R, OH, OR, O, :CHR, :CH2, CH2CO2R, CH2CO2H, CH2SO2R, OSO2R, CO2R, COR, and cyano; optionally double bond in ring; R6, R7, R8, and R9 = H, R, OH, OR, halo, NO2, amino, Me3Sn; or R7R8 = O(CH2)1-2O; R11 = H or R; Q = S, O, or NH; L = linking group or bond; Sup = solid support; or where 1 or more of R2, R3, R6, R7 and R8 = independently = H-(T)n-X-Y-A- where: X = CO, NH, S or O; T = combinatorial unit; Y = divalent group such that HY = R; A = O, S, NH, or bond; and n = pos. integer]. The compds. are intermediates for pyrrolobenzodiazepine derivs. II, which are claimed as being potentially useful for treatment of bacterial, parasitic, viral, and gene-based diseases. For example, the supported chloroformate ester III underwent (1) elaboration with 4,5-dimethoxyanthranilic acid, (2) amidation with 2-pyrrolidinemethanol, and (3) oxidative cyclization using SO3.pyridine and DMSO, to give the invention compd. IV. Photochem. cleavage of IV gave the corresponding aminal, which was dehydrated in situ to give the corresponding compd. V. The cleavage product showed cytotoxicity against human leukemia cells which was identical to that of authentic samples of V. Another compd. I was derivatized at a sidechain using 3 amino acids in 3 chain positions to give a 27-member combinatorial library.

IT **260417-41-2DP**, derivs.
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(combinatorial library; solid-phase prepn. and combinatorial libraries of pyrrolobenzodiazepine derivs. for drug screening)

RN 260417-41-2 CAPLUS

CN Glycinamide, glycylglycyl-N-[3-[[(11R,11aR)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-[(phenylmethoxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]- (9CI) (CA INDEX NAME)

Relative stereochemistry.



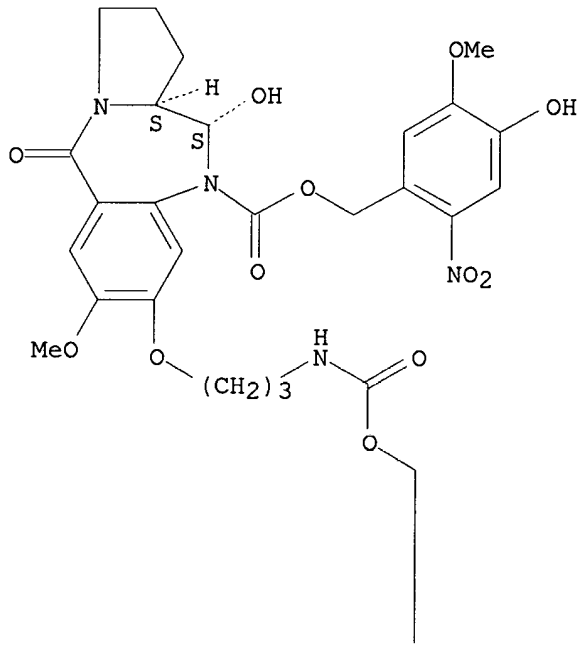
IT **260417-22-9DP**, resin-bound **260417-23-0DP**, resin-bound **260417-30-9DP**, resin-bound **260417-35-4DP**, resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; solid-phase prepn. and combinatorial libraries of pyrrolobenzodiazepine derivs. for drug screening)

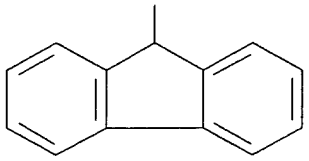
RN 260417-22-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

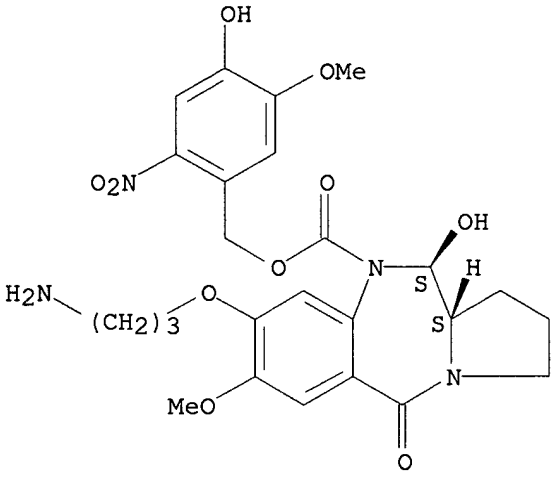
PAGE 1-A



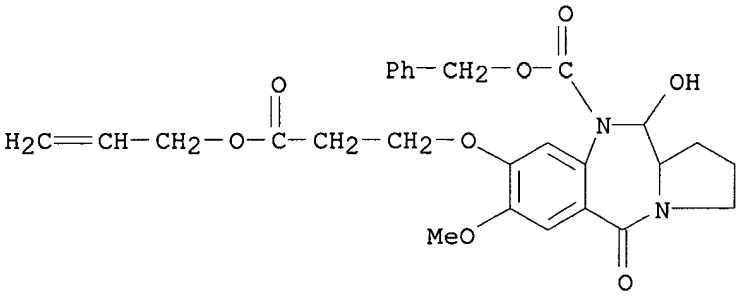


RN 260417-23-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(3-aminopropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

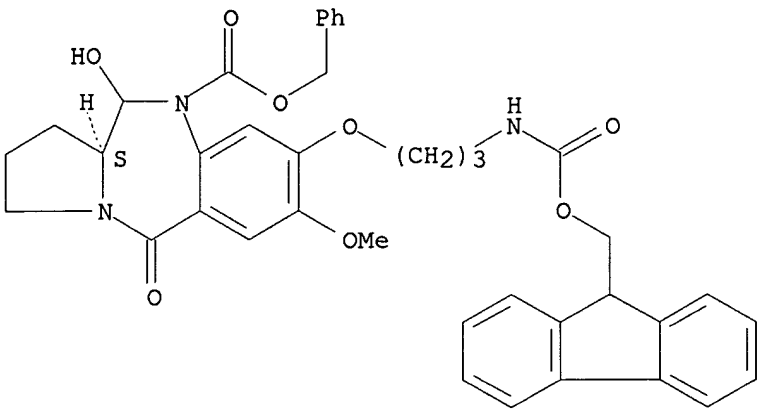


RN 260417-30-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, phenylmethyl ester (9CI) (CA INDEX NAME)



RN 260417-35-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, phenylmethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



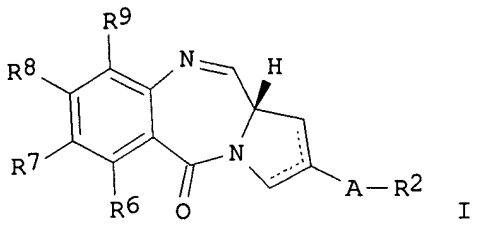
L4 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:161284 CAPLUS
DOCUMENT NUMBER: 132:207851
TITLE: Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 258 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012508	A2	20000309	WO 1999-GB2838	19990827
WO 2000012508	A3	20000921		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9956351	A1	20000321	AU 1999-56351	19990827
EP 1109812	A2	20010627	EP 1999-943066	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1193270	A2	20020403	EP 2001-129700	19990827
EP 1193270	A3	20020417		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525285	T2	20020813	JP 2000-571054	19990827

PRIORITY APPLN. INFO.:
GB 1998-18733 A 19980827
GB 1999-1929 A 19990128
EP 1999-943066 A3 19990827
WO 1999-GB2838 W 19990827

09763813

OTHER SOURCE(S): MARPAT 132:207851
GI



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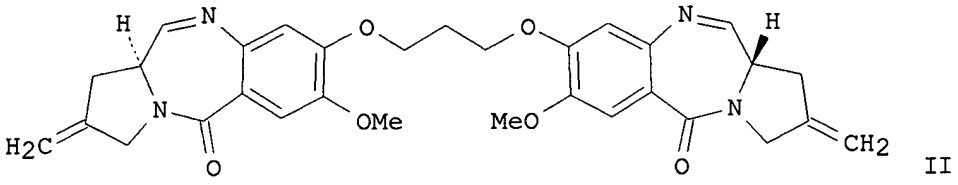


II

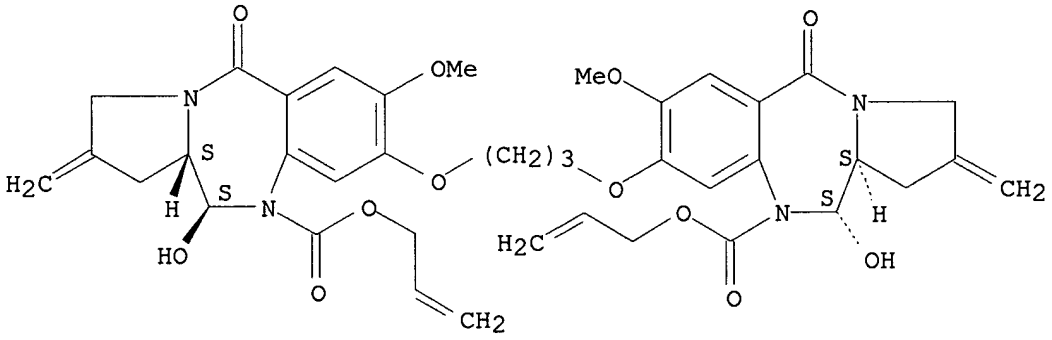
AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein A = CH2 or a single bond; R = (un)substituted (ar)alkyl, (ar)alkenyl, or (ar)alkynyl; R2 = R, OH, OR, CO2H, CO2R, COH, COR, SO2R, CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NHR, NO2, SnMe3; or the compd. is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -X-R'-X- bridge, where R' is an alkylene chain which may contain .gtoreq. 1 heteroatoms and/or arom. rings and/or carbon-carbon double or triple bonds, and each X = independently O, S, or N] were prepd. for the treatment of gene-based diseases, e.g. neoplastic diseases and Alzheimer's disease, and also bacterial, parasitic, and viral infections. For example, II was synthesized in a 6-step sequence. 1',3'-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (prepn. given) was bisamidated with (2S)-2-(tert-butyldimethylsilyloxymethyl)-4-methylenepyrrolidine (74%). TBAF-mediated cleavage of the silyl protecting groups (94%), followed by redn. of the nitro groups by NH2NH2 in the presence of Raney Ni (63%) and N-acylation with allyl chloroformate (50%), gave the protected diamine. Ring closure was accomplished under Swern oxidn. conditions, (COCl)2-DMSO and TEA, (32%). Finally, the imine was formed from the carbinolamine by N-deprotection using Pd(PPh3)4 and elimination of H2O (77%). Both large scale in vitro cytotoxicity cell screens and and in vivo hollow fiber and human tumor xenograft assays were performed on selected compds. of the invention. For instance, II exhibited potent and selective cytotoxicity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75, and the melanoma cell lines MALME-3M (very potent, 0.08 .mu.M) and UACC-62 (very potent, 0.07 .mu.M). In human xenograft studies against five types of tumors, II demonstrated anticancer activity with mixed toxicity results. In addn., II was shown to be the most potent DNA-stabilizing agent known to date according to a DNA helix melting temp. assay. The IC50 value for II in the A2780 human ovarian carcinoma cell line was only 23 pM, a 320-fold increase in cytotoxicity compared to the known antitumor agent DSB-120 (IC50 = 5.2 nM). Remarkably, II was also almost 9000-fold more potent in the cisplatin-resistant A2780cisR cell line (IC50 = 24 pM) than DSB-120 (IC50 = 0.21 mM), suggesting that II may have potential in the treatment of cisplatin-refractory disease.

IT **232931-64-5P 260418-31-3P 260418-44-8P**

260420-49-3P 260420-55-1P 260420-61-9P
260420-67-5P 260420-74-4P 260421-18-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

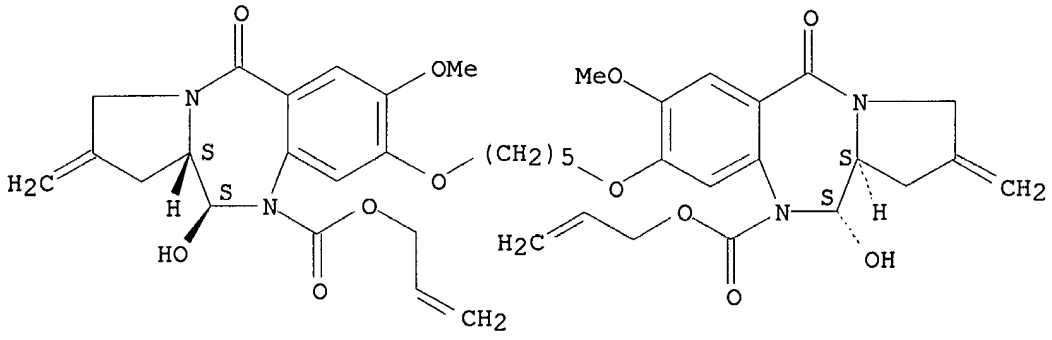
RN 232931-64-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



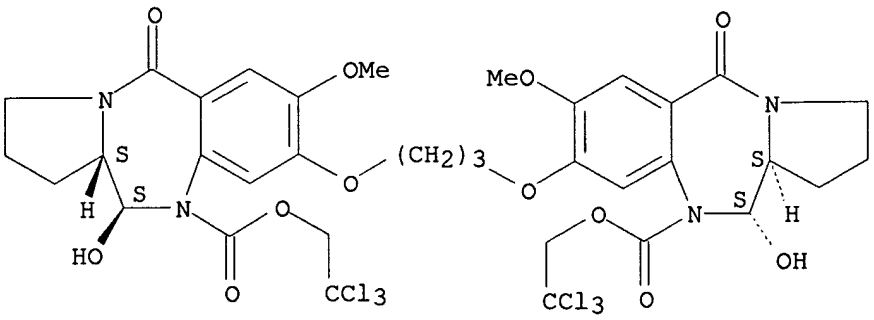
RN 260418-31-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



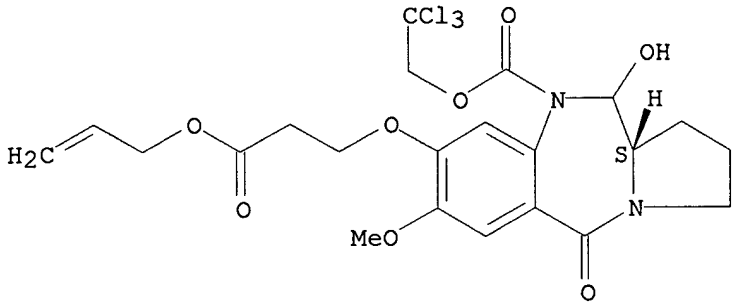
RN 260418-44-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



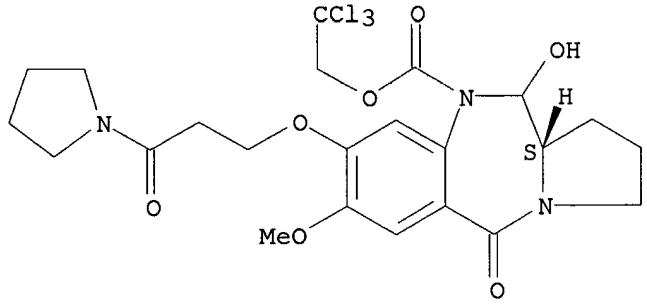
RN 260420-49-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



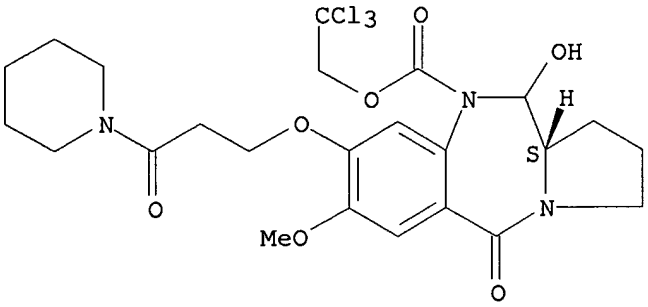
RN 260420-55-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(1-pyrrolidinyl)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



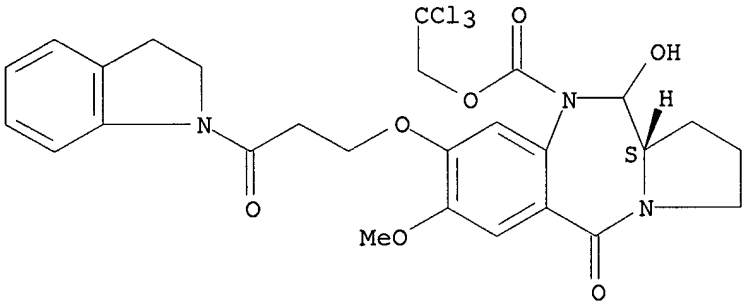
RN 260420-61-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(1-piperidinyl)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



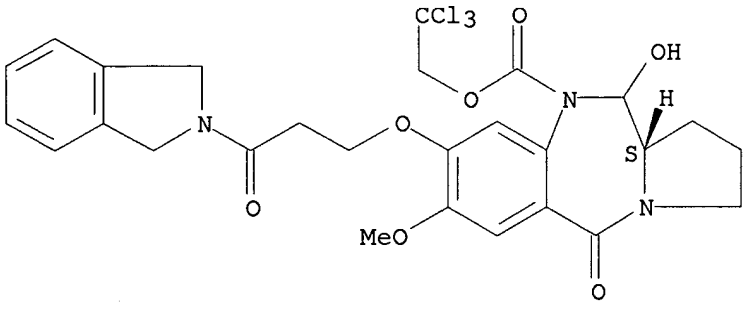
RN 260420-67-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-(2,3-dihydro-1H-indol-1-yl)-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 260420-74-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-(1,3-dihydro-2H-isoindol-2-yl)-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

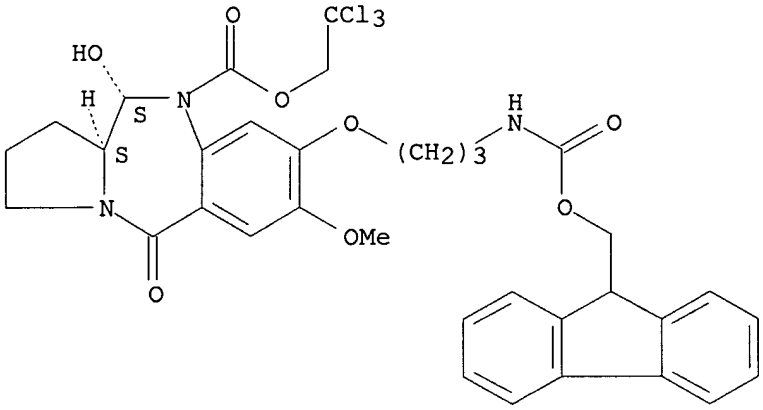
Absolute stereochemistry.



RN 260421-18-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

8-[3-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

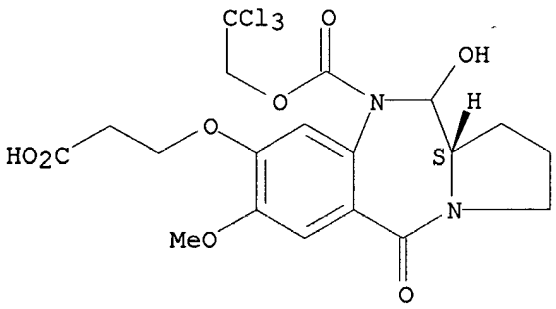


IT **260417-65-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(target compd.; prepn. of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 260417-65-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(2,2,2-trichloroethyl) ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:161283 CAPLUS

DOCUMENT NUMBER: 132:207703

TITLE: Preparation of pyrrolobenzodiazepines (PBDs) as antitumor antibiotics

INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson

PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK

SOURCE: PCT Int. Appl., 101 pp.

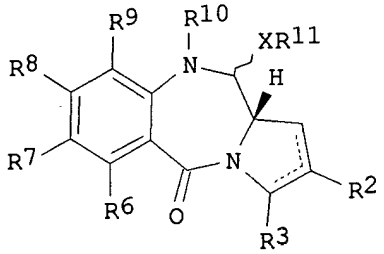
09763813

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012507	A2	20000309	WO 1999-GB2837	19990827
WO 2000012507	A3	20000831		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9955261	A1	20000321	AU 1999-55261	19990827
EP 1109811	A2	20010627	EP 1999-941766	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525284	T2	20020813	JP 2000-571053	19990827

PRIORITY APPLN. INFO.: GB 1998-18731 A 19980827
WO 1999-GB2837 W 19990827

OTHER SOURCE(S): MARPAT 132:207703
GI



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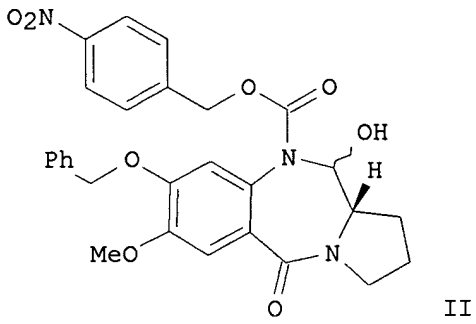


II

AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein R = (un)substituted (ar)alkyl, etc.; R2 and R3 = independently H, R, OH, OR, =O, =CH-R, =CH2, CH2-CO2R, CH2-CO2H, CH2-SO2R, O-SO2-R, CO2R, COR, or CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NO2, or Me3Sn; or R7 and R8 together form a -O-(CH2)p-O- group, where p = 1 or 2; or the compd. is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -T-R'-T- bridge, where R' is an alkylene chain which may contain .gtoreq. 1 heteroatoms and/or arom. rings and/or carbon-carbon double or triple bonds, and each T = independently O, S, or N; R10 = a therapeutically removable N-protecting group; R11 = H or R; X is S, O, or NH] were prepd. for the treatment of cancer and other site-specific diseases where a local increase of toxicity is beneficial to the patient. Examples include the syntheses of benzyl DC-81, benzyl tomaymycin, and DSB-120 prodrugs starting from

2-nitrobenzoic acid derivs. and pyrrolidines. Data from enzyme and light activation studies and cytotoxicity assays are also given. For example, the nitroreductase-activated benzyl DC-81 (II) was formed in a 6-step sequence involving: (1) benzylation of vanillic acid (67%); (2) ring nitration (82%); (3) amidation with (2S)-pyrrolidinemethanol (88%); (4) redn. of the nitro group (81%); (5) N-addn. of 4-nitrobenzyl chloroformate; and (6) cyclization using Swern oxidn. conditions (31%). In the presence of nitroreductase and the NADH co-factor, II demonstrated antitumor activity (IC50 = 1-5 .mu.M) against the SW1116 and LS174T human adenocarcinoma colonic cell lines. II proved non-toxic in SW1116 cells at concns. .ltoreq. 500 .mu.M and showed slight toxicity in LS174T cells at concns. > 100 .mu.M. I may also be suitable for treating bacterial, parasitic, or viral infections by exploiting a unique enzyme produced at the site of infection which is not natural to the host, or by exploiting an elevation in the amt. of an enzyme which does occur naturally in the host.

IT **260391-43-3P 260391-44-4P 260391-45-5P**

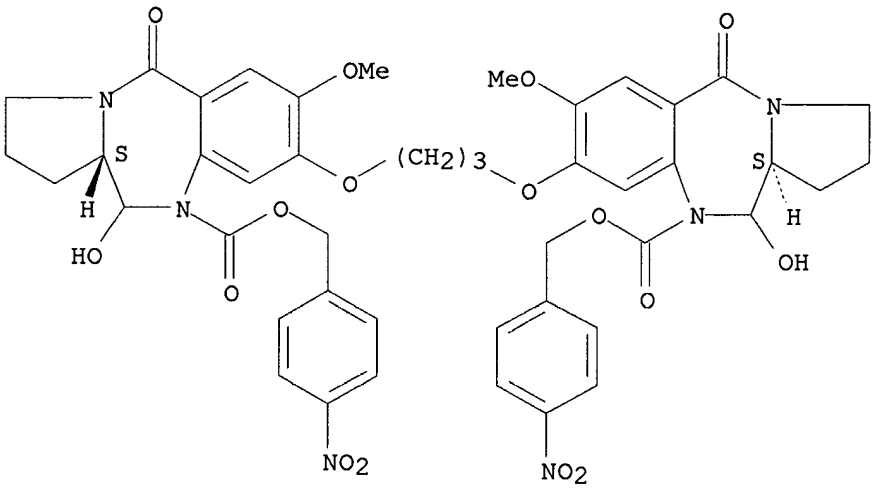
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compd.; prepn. of pyrrolobenzodiazepinone prodrugs from 2-nitrobenzoic acid derivs. and pyrrolidines for the treatment of cancer)

RN 260391-43-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

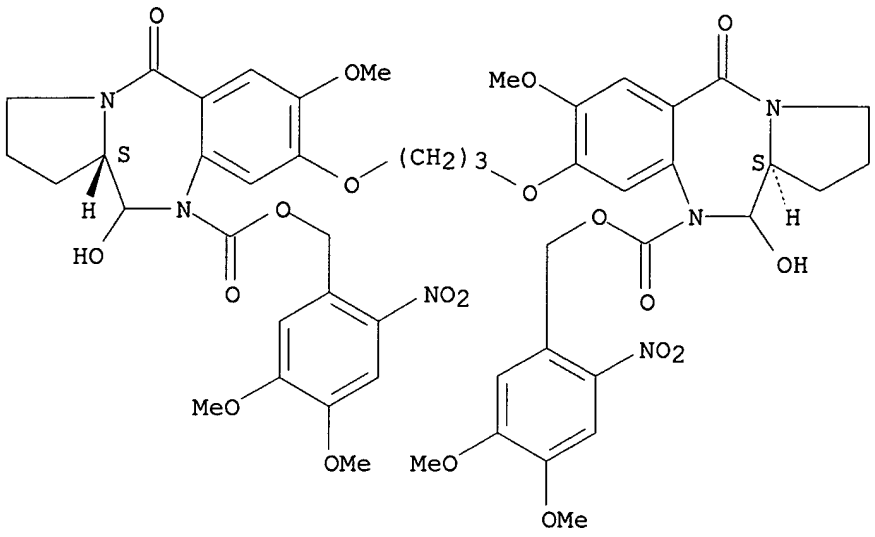


RN 260391-44-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

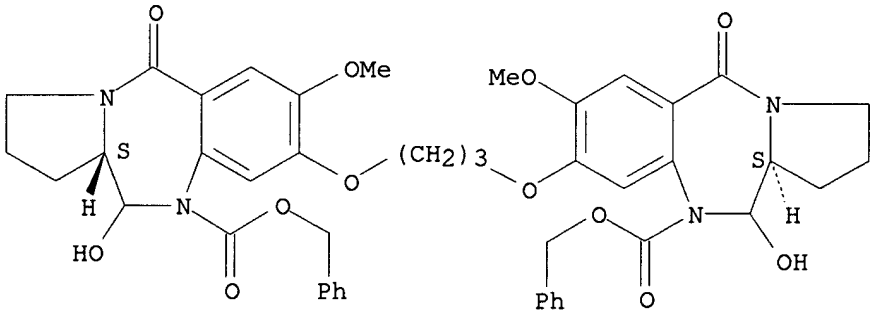
Absolute stereochemistry.

09763813



RN 260391-45-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(phenylmethyl) ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:161282 CAPLUS
DOCUMENT NUMBER: 132:208134
TITLE: Preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012506	A2	20000309	WO 1999-GB2836	19990827

WO 2000012506 A3 20000629
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9955260 A1 20000321 AU 1999-55260 19990827
EP 1107969 A2 20010620 EP 1999-941765 19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2002525283 T2 20020813 JP 2000-571052 19990827
PRIORITY APPLN. INFO.: GB 1998-18730 A 19980827
WO 1999-GB2836 W 19990827
OTHER SOURCE(S): MARPAT 132:208134
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

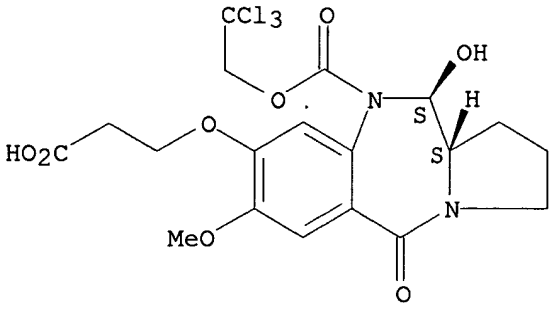
AB Benzodiazepines I [X = CO2H, NH2 or protected amino, SH, OH; A = O, S, NH, or a single bond; R2, R3 = H, R, OH, OR, :O, :CHR, :CH2, CH2CO2R, CH2CO2H, CH2SO2R, OSO2R, CO2R, COR, CN, where R = alkyl, alkenyl, alkynyl, aralkyl, (un)substituted aryl; there is optionally a double bond between C1 and C2 or C2 and C3; R6, R7, R9 = H, R, OH, OR, halo, nitro, amino, Me3Sn; R11 = H or R; Q = S, O or NH; R10 is a nitrogen-protecting group; Y is a divalent group such that HY = R] were prepd. and incorporated into peptides for use as pharmaceuticals. Thus, pyrrolo[2,1-c][1,4]benzodiazepine deriv. II (Fmoc = fluorenylmethoxycarbonyl) was prepd. and applied to the synthesis of a 27-member glycine/valine/phenylalanine tripeptide library which was screened for inhibition of leukemia cells.

IT **256949-59-4P 260449-57-8P 260449-60-3P**
260449-61-4P 260449-63-6P 260449-64-7P
260449-66-9P 260449-67-0P 260450-78-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of peptidyl pyrrolobenzodiazepines as pharmaceuticals)

RN 256949-59-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(2,2,2-trichloroethyl) ester, (11S,11aS)- (9CI) (CA INDEX NAME)

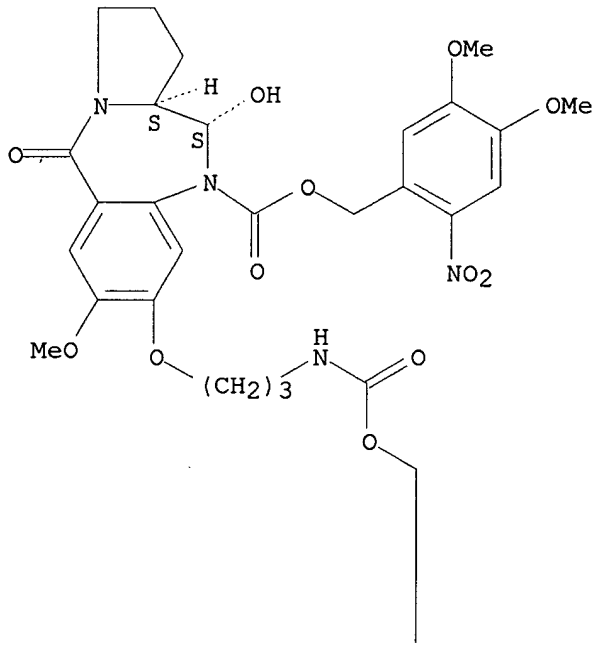
Absolute stereochemistry. Rotation (+).



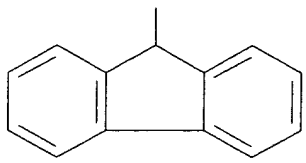
RN 260449-57-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

PAGE 1-A



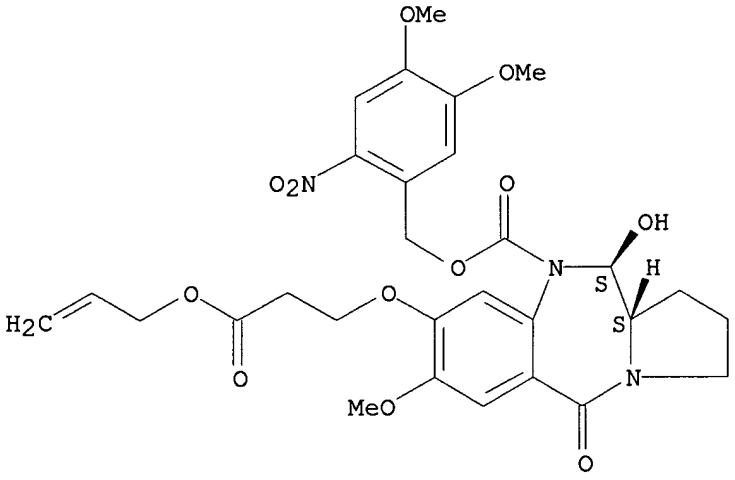
PAGE 2-A



RN 260449-60-3 CAPLUS

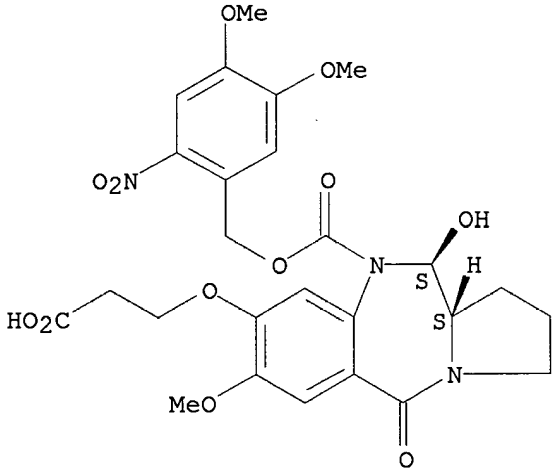
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



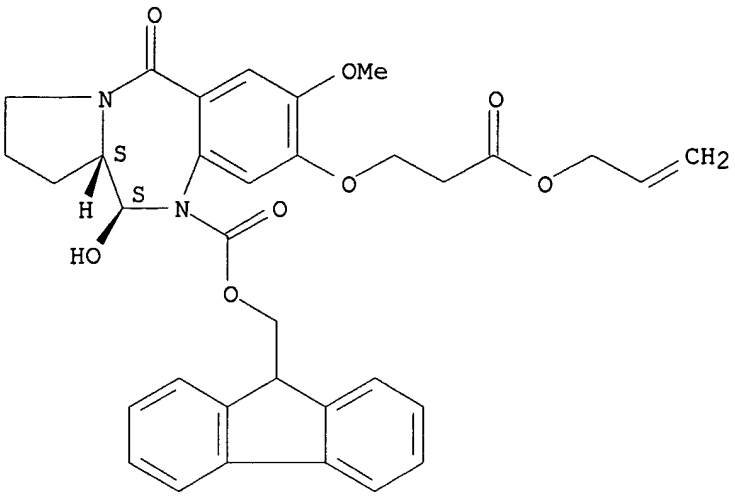
RN 260449-61-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



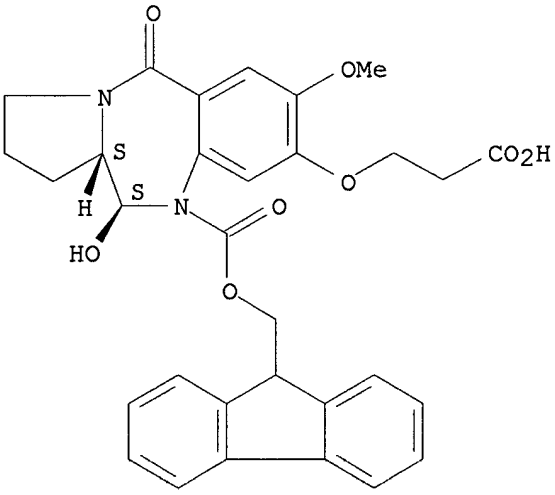
RN 260449-63-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 9H-fluoren-9-ylmethyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



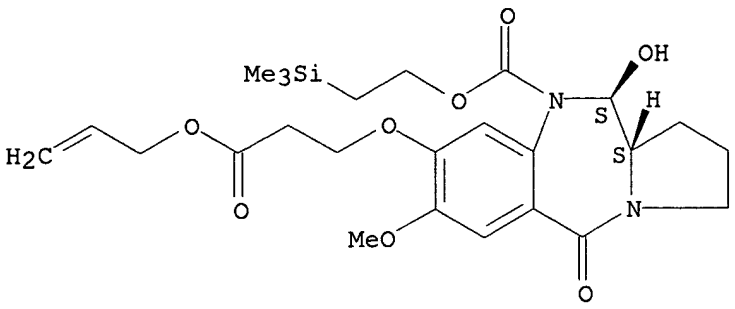
RN 260449-64-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(9H-fluoren-9-ylmethyl) ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



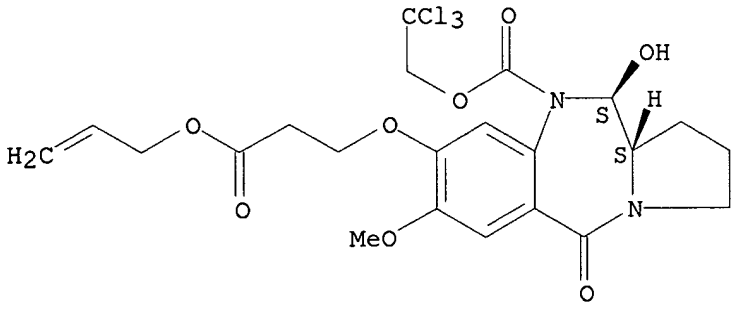
RN 260449-66-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 2-(trimethylsilyl)ethyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



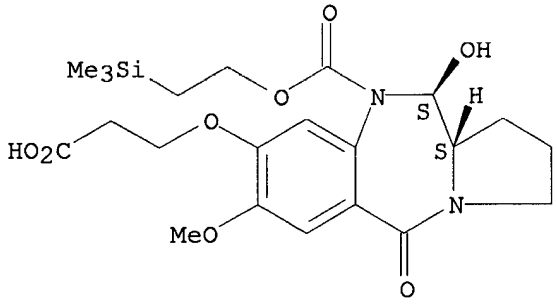
RN 260449-67-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 260450-78-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-[2-(trimethylsilyl)ethyl] ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

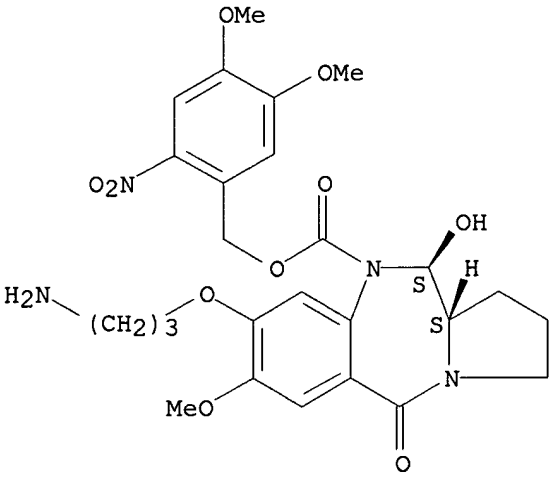


IT **260449-58-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of peptidyl pyrrolobenzodiazepines as pharmaceuticals)
RN 260449-58-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(3-aminopropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,

09763813

(4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:758546 CAPLUS
DOCUMENT NUMBER: 132:137361
TITLE: Synthesis, in Vitro Antiproliferative Activity, and DNA-Binding Properties of Hybrid Molecules Containing Pyrrolo[2,1-c][1,4]benzodiazepine and Minor-Groove-Binding Oligopyrrole Carriers
AUTHOR(S): Baraldi, Pier Giovanni; Balboni, Gianfranco; Cacciari, Barbara; Guiotto, Andrea; Manfredini, Stefano; Romagnoli, Romeo; Spalluto, Giampiero; Thurston, David E.; Howard, Philip W.; Bianchi, Nicoletta; Rutigliano, Cristina; Mischiati, Carlo; Gambari, Roberto
CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche e Dipartimento di Biochimica e Biologia Molecolare, Universita di Ferrara, Ferrara, 44100, Italy
SOURCE: Journal of Medicinal Chemistry (1999), 42(25), 5131-5141
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:137361

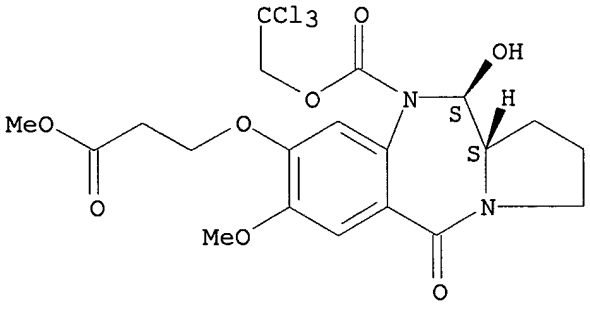
AB The synthesis, biol. activity, and DNA-binding properties of a series of four pyrrolo[2,1-c][1,4]benzodiazepine (PBD) hybrids contg. polypyrrole side chains are described and structure-activity relationships examd. To investigate sequence selectivity and stability of drug/DNA complexes, DNase I footprinting and arrested polymerase chain reaction (PCR) were performed on human c-myc oncogene, estrogen receptor gene, and human immunodeficiency virus type 1 long terminal repeat (HIV-1 LTR) gene sequences. The antiproliferative activity of the hybrids was tested in vitro on human myeloid leukemia K562 and T-lymphoid Jurkat cell lines and compared to antiproliferative effects of the natural product distamycin A 1, its tetrapyrrole homolog, DC 81, and a PBD ester. The new hybrids exhibit different DNA-binding activity with respect to both distamycin A 1 and the parent PBD. In addn., a direct relationship was found between the

no. of pyrrole rings present in the hybrids and the stability of drug/DNA complexes. With respect to antiproliferative effects, it was found that the increase in the length of the polypyrrole backbone leads to an increase of in vitro antiproliferative effects, i.e., the hybrid with 4 pyrroles is more active than the other ones both against K562 and Jurkat cell lines.

IT **219562-65-9P 256949-59-4P 256949-63-0P**
256949-64-1P 256949-65-2P 256949-66-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn., antiproliferative activity, and DNA-binding pyrrolobenzodiazepines contg. oligopyrrole carriers)

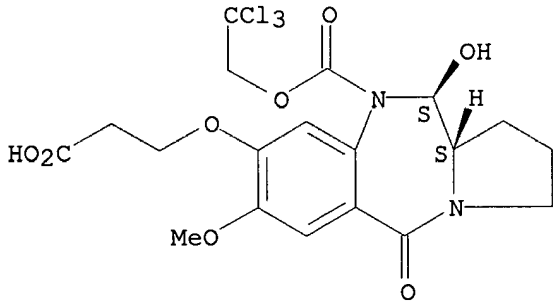
RN 219562-65-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(3-methoxy-3-oxopropoxy)-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



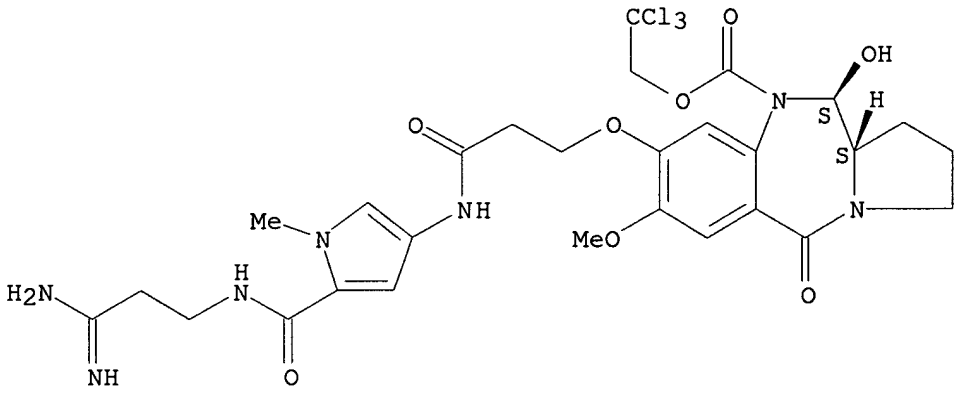
RN 256949-59-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(2,2,2-trichloroethyl) ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 256949-63-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

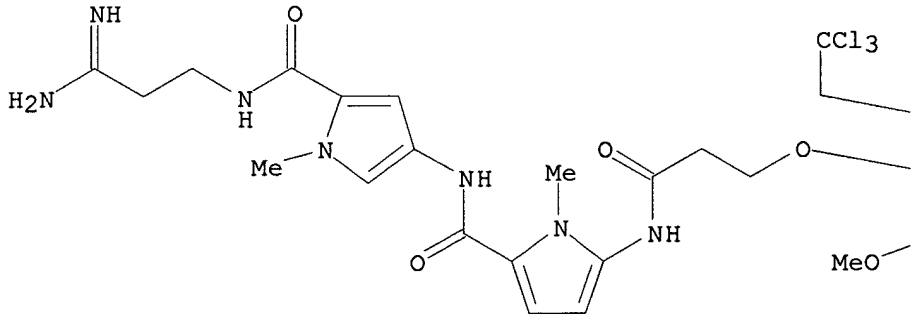


● HCl

RN 256949-64-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

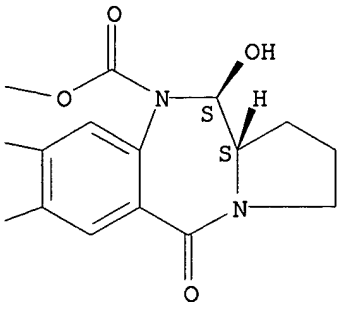
Absolute stereochemistry.

PAGE 1-A



● HCl

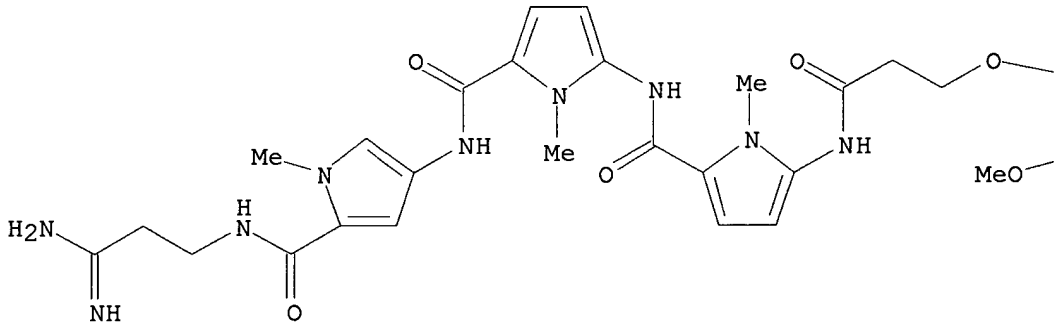
PAGE 1-B



RN 256949-65-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

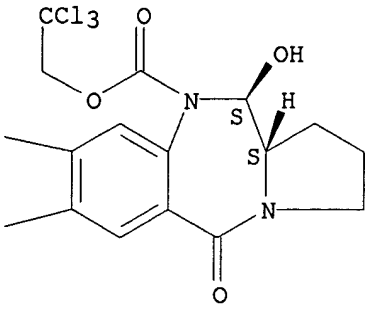
Absolute stereochemistry.

PAGE 1-A



● HCl

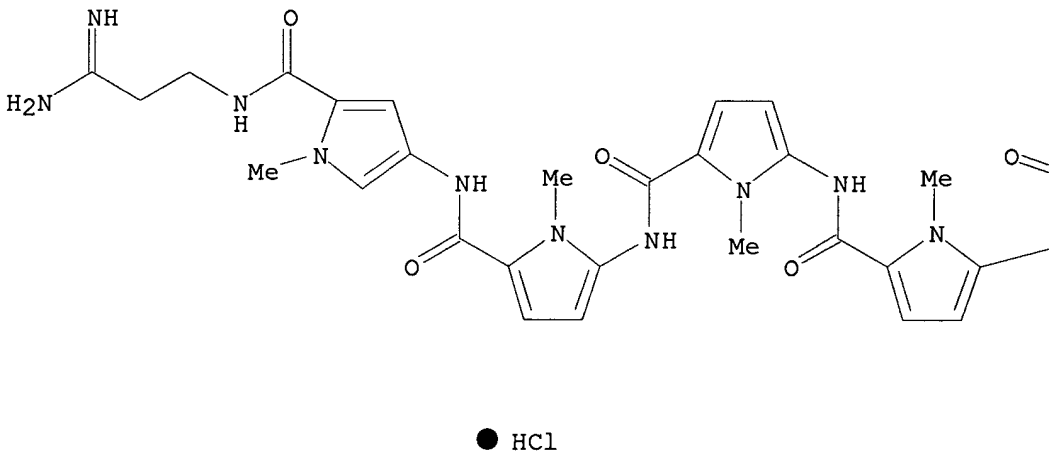
PAGE 1-B



RN 256949-66-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

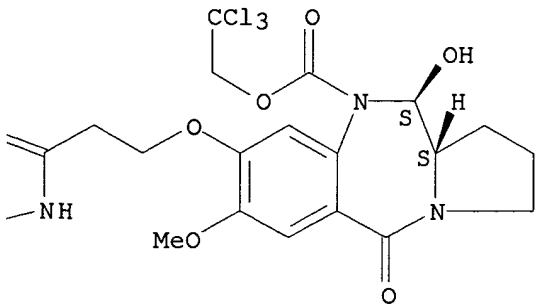
Absolute stereochemistry.

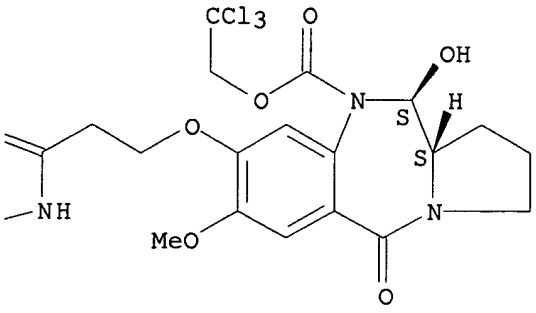
PAGE 1-A



● HCl

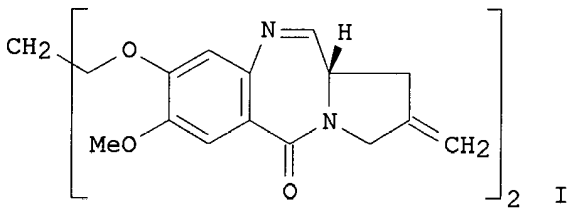
PAGE 1-B





REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:273645 CAPLUS
DOCUMENT NUMBER: 131:116218
TITLE: Synthesis of a novel C2/C2'-exo unsaturated pyrrolobenzodiazepine cross-linking agent with remarkable DNA binding affinity and cytotoxicity
AUTHOR(S): Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.; Jenkins, Terence C.; Kelland, Lloyd R.
CORPORATE SOURCE: School of Pharmacy and Biomedical Sciences, CRC Gene Targeted Drug Design Research Group, University of Portsmouth, Portsmouth, Hants, PO1 2DT, UK
SOURCE: Chemical Communications (Cambridge) (1999), (9), 797-798
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



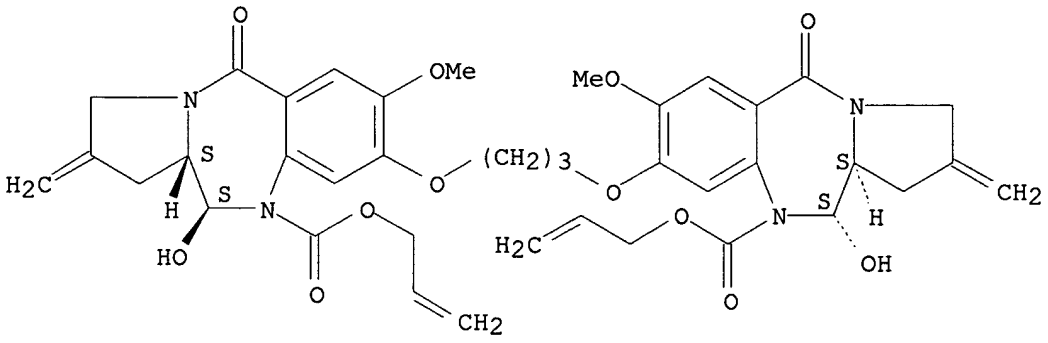
AB A C2/C2'-exo unsatd. pyrrolobenzodiazepine dimer (I) has been synthesized which is cytotoxic at the picomolar level and has remarkable covalent DNA binding affinity, raising the melting temp. of duplex-form calf thymus DNA by 34 after 18 h incubation.

IT **232931-64-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)

RN 232931-64-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-

methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

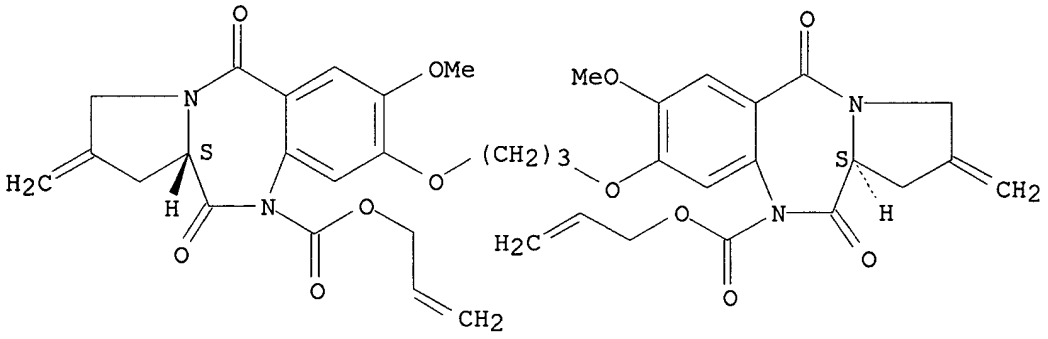


IT **232931-66-7P 232931-67-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)

RN 232931-66-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5,11-dioxo-, di-2-propenyl ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

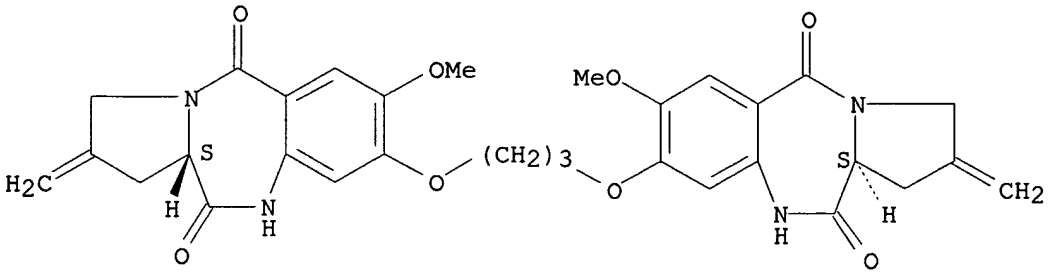
Absolute stereochemistry.



RN 232931-67-8 CAPLUS

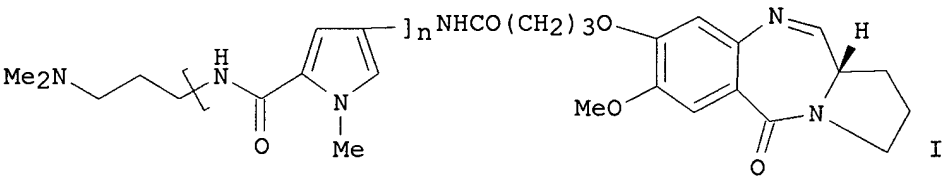
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:777202 CAPLUS
DOCUMENT NUMBER: 130:125384
TITLE: Design and Synthesis of Novel Pyrrolo[2,1-c][1,4]benzodiazepine-Lexitropsin Conjugates
AUTHOR(S): Damayanthi, Yalamati; Reddy, B. S. Praveen; Lown, J. William
CORPORATE SOURCE: Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Can.
SOURCE: Journal of Organic Chemistry (1999), 64(1), 290-292
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:125384
GI

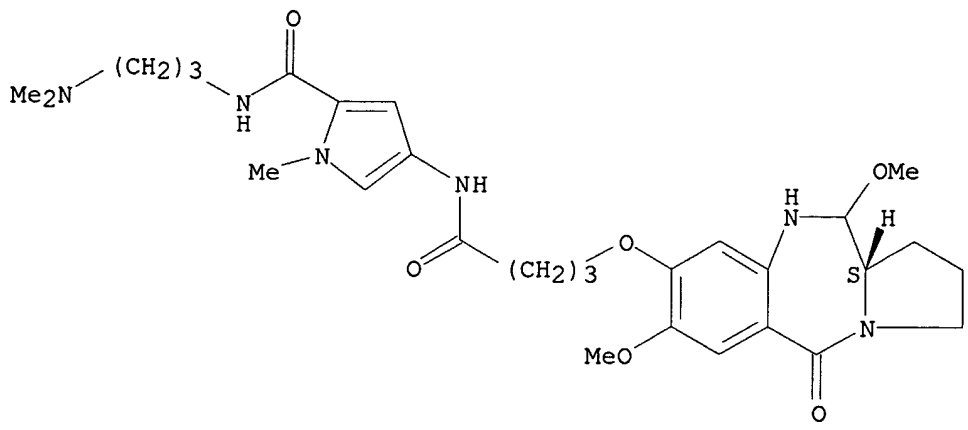


AB A versatile and convenient strategy for the design and synthesis of a series of novel pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-lexitropsin conjugates I (n = 1-3) bonded through the C8 position with a suitable linker of three carbons (overall five-atom spacer) is described. I were designed in order to examine the combined effect of both moieties on DNA sequence selective binding ability and cytotoxicity (no data).

IT **219931-77-8P 219931-78-9P 219931-79-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(design and synthesis of pyrrolobenzodiazepine-lexitropsin conjugates)

RN 219931-77-8 CAPLUS
CN 1H-Pyrrole-2-carboxamide, N-[3-(dimethylamino)propyl]-4-[[4-[[(11aS)-2,3,5,10,11,11a-hexahydro-7,11-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-1-oxobutyl]amino]-1-methyl- (9CI) (CA INDEX NAME)

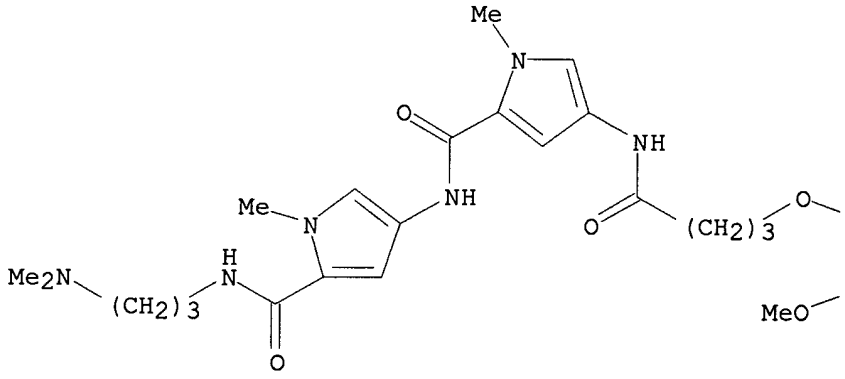
Absolute stereochemistry.



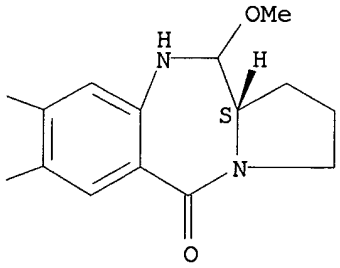
RN 219931-78-9 CAPLUS
CN 1H-Pyrrole-2-carboxamide, N-[5-[[[3-(dimethylamino)propyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[4-[[(11aS)-2,3,5,10,11,11a-hexahydro-7,11-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-1-oxobutyl]amino]-1-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

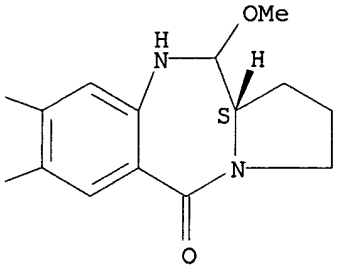
PAGE 1-A



PAGE 1-B



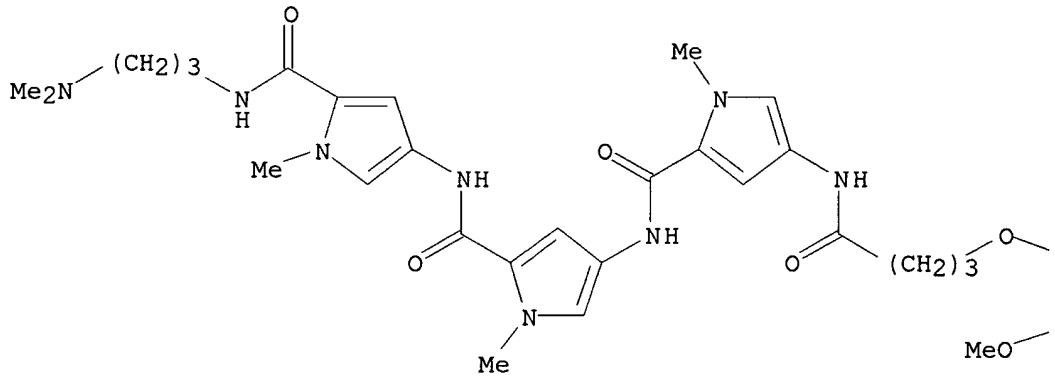
PAGE 1-B

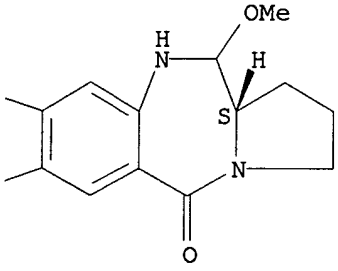


RN 219931-79-0 CAPLUS
CN 1H-Pyrrole-2-carboxamide, N-[5-[[[3-(dimethylamino)propyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[[4-[[(11aS)-2,3,5,10,11,11a-hexahydro-7,11-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-1-oxobutyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

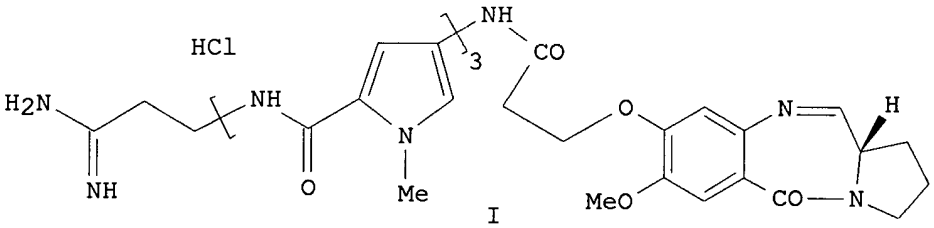




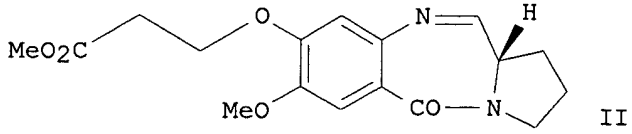
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:760824 CAPLUS
DOCUMENT NUMBER: 130:95405
TITLE: Design, synthesis and biological activity of a pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid
AUTHOR(S): Baraldi, Pier Giovanni; Cacciari, Barbara; Guiotto, Andrea; Leoni, Alberto; Romagnoli, Romeo; Spalluto, Giampiero; Mongelli, Nicola; Howard, Philip W.; Thurston, David E.; Bianchi, Nicoletta; Gambari, Roberto
CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche, Universita di Ferrara, Ferrara, 44100, Italy
SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(21), 3019-3024
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:95405
GI



I



II

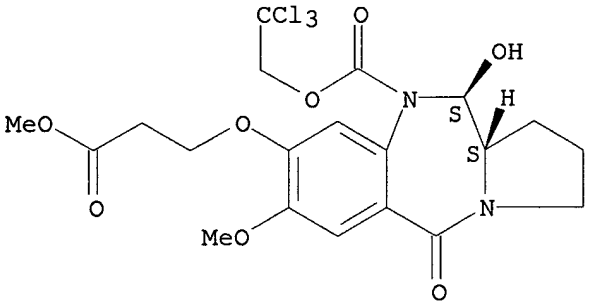
AB The authors report the synthesis of a new hybrid (I) which is a combination of the naturally occurring antitumor agent distamycin A and the pyrrolo[2,1-c][1,4]benzodiazepine (II), related to naturally occurring anthramycin. The antitumor activity of the hybrid I was tested in vitro and compared to the natural product distamycin A and the PBD II.

IT **219562-65-9P 219562-76-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis and biol. activity of a pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid)

RN 219562-65-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(3-methoxy-3-oxopropoxy)-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

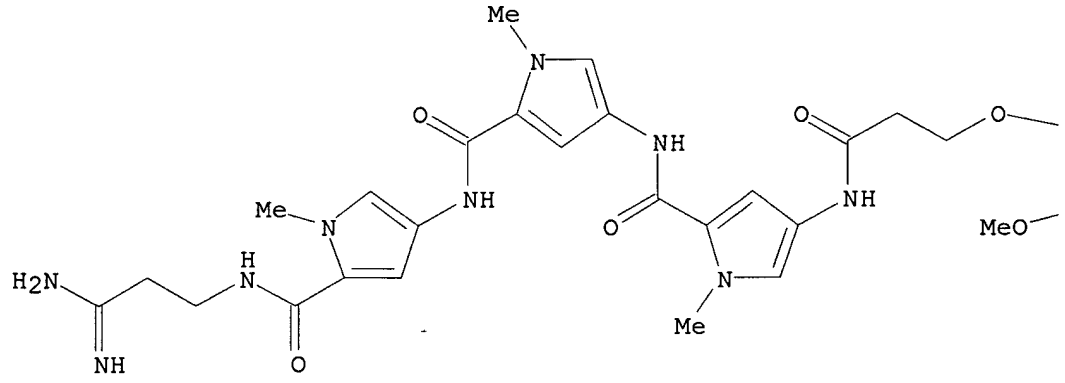


RN 219562-76-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

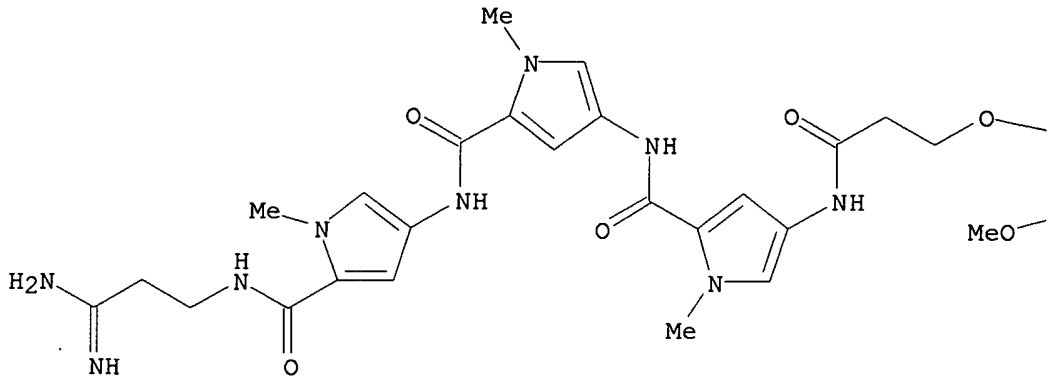
Absolute stereochemistry.

PAGE 1-A



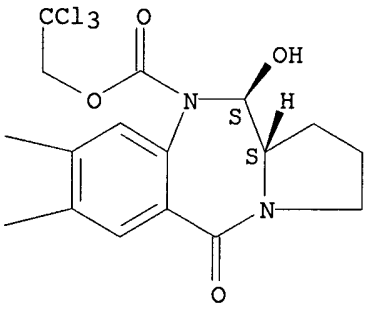
● HCl

PAGE 1-A



● HCl

PAGE 1-B



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:644058 CAPLUS
DOCUMENT NUMBER: 126:8088
TITLE: Synthesis of Sequence-Selective C8-Linked Pyrrolo[2,1-c][1,4]benzodiazepine Interstrand DNA Crosslinking Agents
AUTHOR(S): Thurston, David E.; Bose, D. Subhas; Thompson, Andrew S.; Howard, Philip W.; Leoni, Alberto; Croker, Stephen J.; Jenkins, Terrence C.; Neidle, Steven; Hartley, John A.; Hurley, Laurence H.
CORPORATE SOURCE: School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth/Hants, PO1 2DT, UK
SOURCE: Journal of Organic Chemistry (1996), 61(23), 8141-8147
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

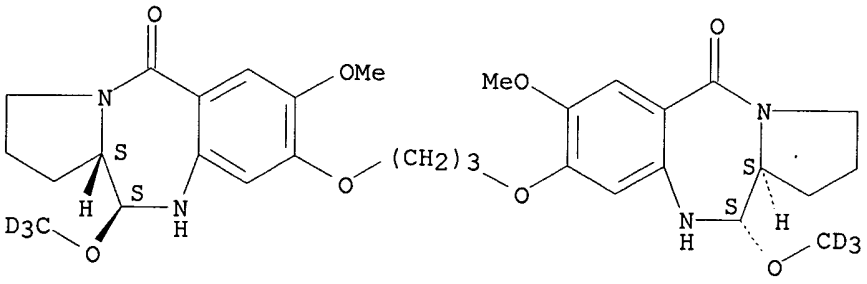
AB An efficient convergent synthesis of a homologous series of C8-linked pyrrolobenzodiazepine dimers with remarkable DNA interstrand crosslinking

activity and potent in vitro cytotoxicity is reported. The "amino thioacetal" cyclization procedure was used to produce the electrophilic DNA-interactive N10-C11 imine moiety during the final synthetic step. In order to construct the key A-ring fragments, a versatile convergent approach has been developed to join two units of vanillic acid with .alpha.,.omega.-dihaloalkanes of varying length to provide the required bis(4-carboxy-2-methoxyphenoxy)alkanes while avoiding the formation of mixts. of monoalkylated and bisalkylated products.

IT **183487-36-7P 183626-03-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

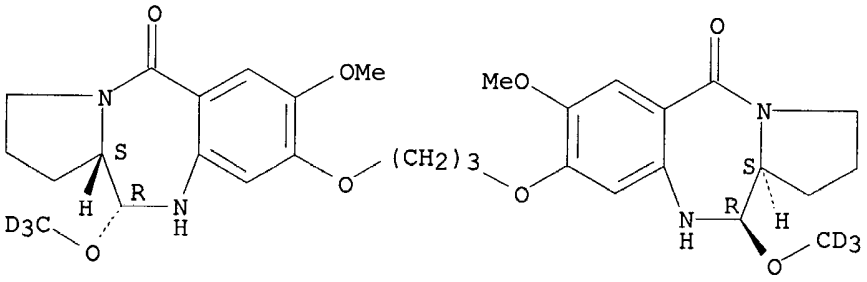
RN 183487-36-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-(methoxy-d3)-, [11S-[8(11'R*,11'aR*),11.alpha.,11a.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 183626-03-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-(methoxy-d3)-, [11R-[8(11'R*,11'aS*),11.alpha.,11a.beta.]]- (9CI) (CA INDEX NAME)

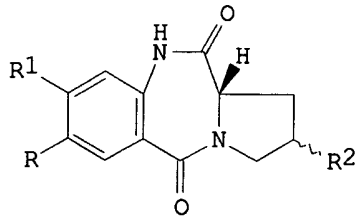
Absolute stereochemistry.



L4 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:114601 CAPLUS
DOCUMENT NUMBER: 114:114601
TITLE: The noncovalent interaction of pyrrolo[2,1-c][1,4]benzodiazepine-5,11-diones with DNA
AUTHOR(S): Jones, G. B.; Davey, C. L.; Jenkins, T. C.; Kamal, A.; Kneale, G. G.; Neidle, S.; Webster, G. D.; Thurston, D. E.
CORPORATE SOURCE: Sch. Pharm. Biomed. Sci., Portsmouth Polytech.,

09763813

Portsmouth, PO1 2DZ, UK
SOURCE: Anti-Cancer Drug Des. (1990), 5(3), 249-64
CODEN: ACDDEA; ISSN: 0266-9536
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



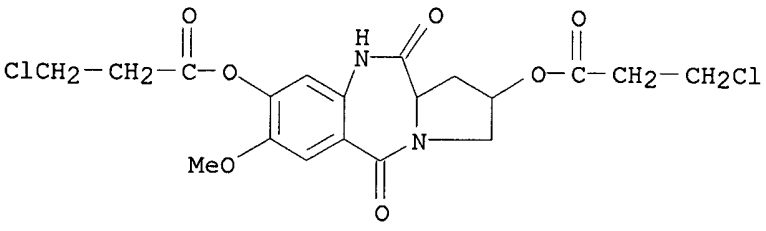
I, R=R1=H, ?-R2
II, R=R1=H, ?-R2
III, R=MeO, R1=?-R2=OAc
IV, R=MeO, R1=R2=OH

AB A series of 15 pyrrolo[2,1-c][1,4]benzodiazepine-5,11-diones [I and II, e.g., R2 = H, OH, OCONH2, or OCO(CH2)2Cl] were prepd. and evaluated for in vitro DNA binding by thermal denaturation and fluorescence quenching studies with calf thymus (CT) DNA. Two compds. of the series, III or IV (.beta.-OH), elevate the m.p. of DNA by 2.9 and 3.3 K, resp. Similarly, a significant quenching of the fluorescence of IV (.beta.-OH) was obsd. upon interaction with CT-DNA. As controls, IV (.alpha.-OH) with the reverse stereochem. at C2 and non-substituted parent dilactam, failed to increase the DNA m.p. or exhibit significant quenching upon interaction with DNA. In addn., preliminary expts. with GC- and AT-rich polymers suggest some sequence-dependent properties for the dilactams III and IV (.beta.-OH). Overall, these results indicate a highly specific structural requirement for DNA binding. Mol. modeling with d(GTAGATC), d(GCAGATC) and d(GCGTAGC) duplex sequences provided a model based on hydrogen bonding between IV (.beta.-OH) and DNA, that rationalizes some of the results obtained. It is possible that the obsd. interactions represent the noncovalent (binding) component of the interaction of covalently-bonding anthramycin-type anti-tumor antibiotics with DNA.

IT **132412-89-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and noncovalent interaction with DNA)

RN 132412-89-6 CAPLUS

CN Propanoic acid, 3-chloro-, 2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-2,8-diyl ester, (2R-cis)- (9CI) (CA INDEX NAME)



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 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09  ZDB will be removed from STN
 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 09  JAPIO to be reloaded August 25, 2002
 NEWS 20  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 21  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 22  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 23  Aug 26  Sequence searching in REGISTRY enhanced

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               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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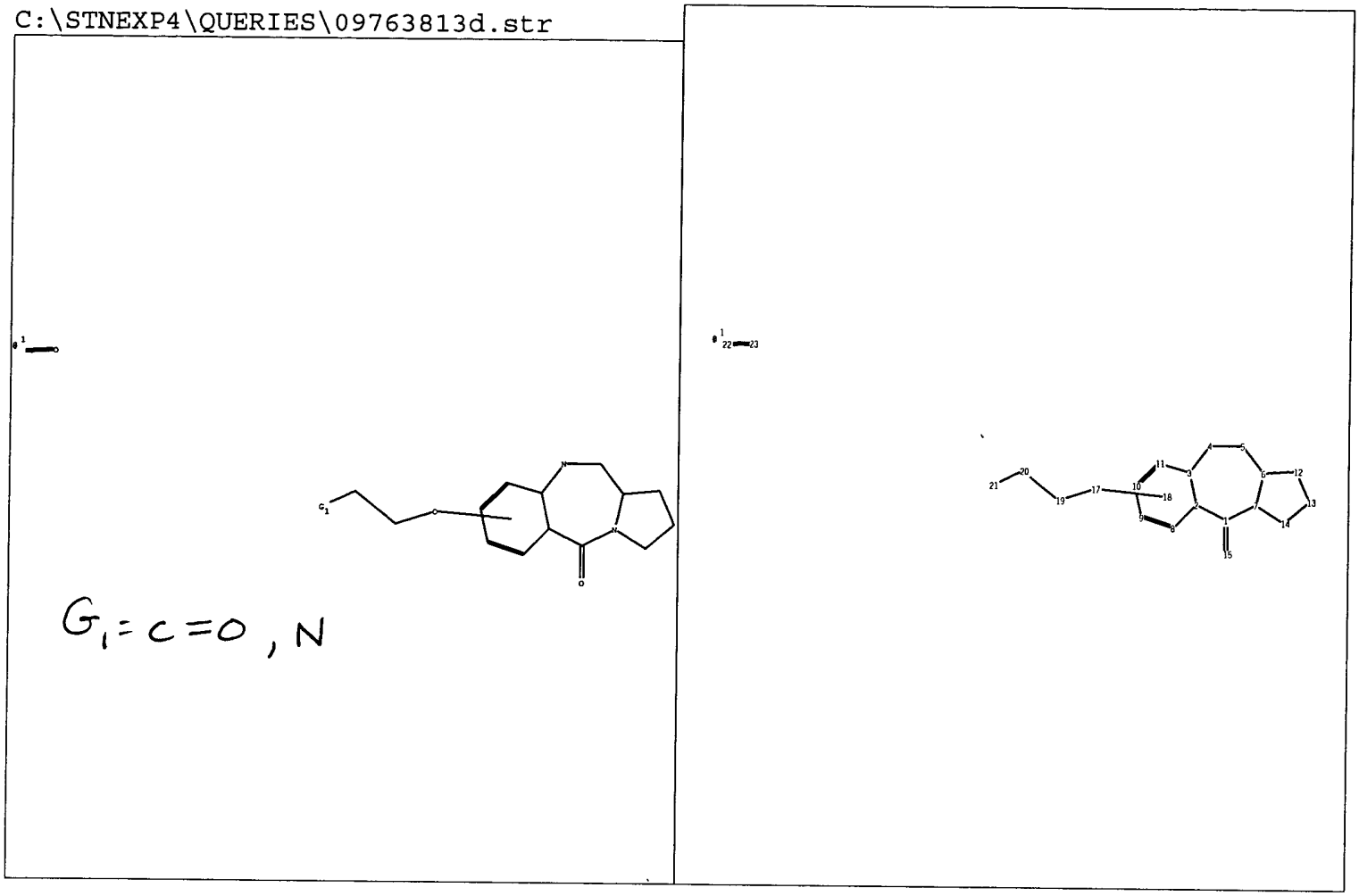

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1-15 17-19 19-20 20-21 22-23
ring bonds :
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10-11 12-13 13-14
exact/norm bonds :
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10-11 12-13 13-14 17-19 20-21 22-23
exact bonds :
19-20
isolated ring systems :
containing 1 :

G1:N,[*1]

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
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19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS

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L1      STRUCTURE UPLOADED

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L1 HAS NO ANSWERS
L1              STR
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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SAMPLE SCREEN SEARCH COMPLETED -     11 TO ITERATE

100.0% PROCESSED      11 ITERATIONS                                0 ANSWERS
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FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           22 TO      418
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

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FULL SCREEN SEARCH COMPLETED - 249 TO ITERATE

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SEARCH TIME: 00.00.01

L3 26 SEA SSS FUL L1

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	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	140.66	140.87

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FILE COVERS 1907 - 3 Sep 2002 VOL 137 ISS 10
FILE LAST UPDATED: 2 Sep 2002 (20020902/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s l3 full
L4 7 L3

=> d l4 1-7 ibib abs hitstr

L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:787600 CAPLUS
DOCUMENT NUMBER: 134:95090
TITLE: Pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid inhibits DNA binding to transcription factor Sp1
AUTHOR(S): Baraldi, P. G.; Cacciari, B.; Guiotto, A.; Romagnoli, R.; Spalluto, G.; Leoni, A.; Bianchi, N.; Feriotto, G.; Rutigliano, C.; Mischiati, C.; Gambari, Roberto
CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche, Universita di Ferrara, Ferrara, 44100, Italy
SOURCE: Nucleosides, Nucleotides & Nucleic Acids (2000), 19(8), 1219-1229
CODEN: NNNAFY; ISSN: 1525-7770
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal

LANGUAGE: English

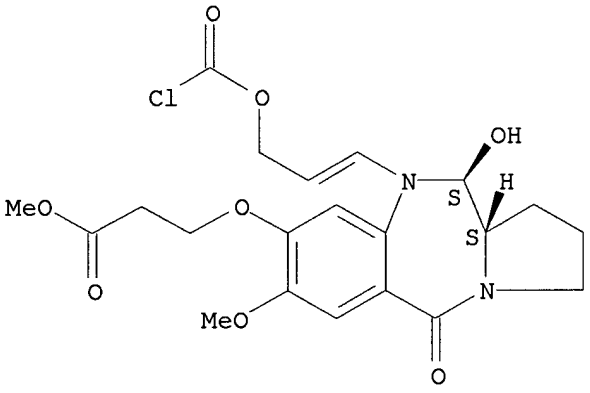
AB The hybrid was designed and synthesized,which was prepd. combining the minor groove binders distamycin A and pyrrolo[2,1-c][1,4]benzodiazepine (PBD) 4, related to the natural occurring anthramycin and DC-81. The effects of the hybrid on mol. interactions between DNA and transcription factor Sp1 were studied. Thus, PBD-distamycin hybrid is a powerful inhibitor of Sp1/DNA interactions.

IT **319477-08-2P 319477-11-7P 319477-13-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pyrrolo[2,1-c][1,4]benzodiazepine-distamycin hybrid inhibits DNA binding to transcription factor Sp1)

RN 319477-08-2 CAPLUS

CN Propanoic acid, 3-[[(11S,11aS)-10-[3-[(chlorocarbonyl)oxy]-1-propenyl]-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-, methyl ester (9CI) (CA INDEX NAME)

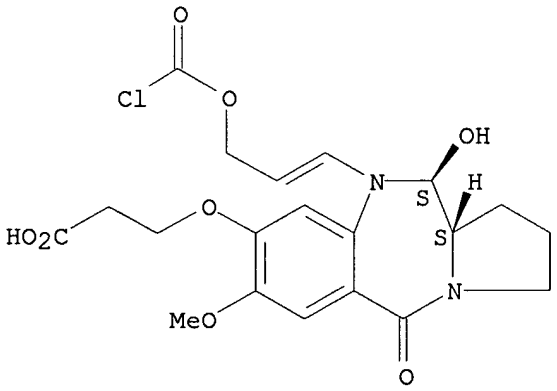
Absolute stereochemistry.
Double bond geometry unknown.



RN 319477-11-7 CAPLUS

CN Propanoic acid, 3-[[(11S,11aS)-10-[3-[(chlorocarbonyl)oxy]-1-propenyl]-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (9CI) (CA INDEX NAME)

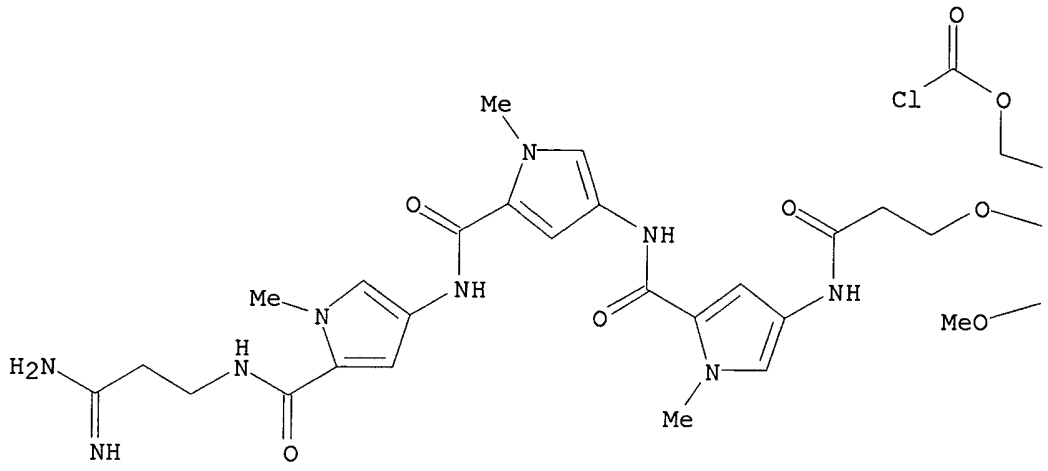
Absolute stereochemistry.
Double bond geometry unknown.



RN 319477-13-9 CAPLUS
CN Carbonochloridic acid, 3-[(11S,11aS)-8-[3-[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]-2-propenyl ester, monohydrochloride (9CI) (CA INDEX NAME)

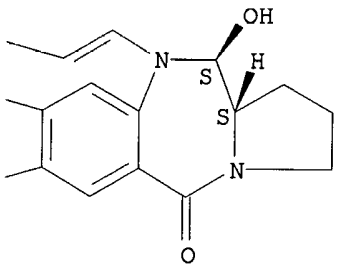
Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



● HCl

PAGE 1-B



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:244166 CAPLUS

09763813

DOCUMENT NUMBER:	133:4639
TITLE:	Synthesis of polyaminoalkyl substituted conjugates of pyrrolo[2,1-c][1,4]benzodiazepine involving SNAr reaction of 2-nitro-5-fluorobenzoate precursors
AUTHOR(S):	Matsumoto, Kiyoshi; Iida, Hirokazu; Lown, J. William
CORPORATE SOURCE:	Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, 606-8501, Japan
SOURCE:	Heterocycles (2000), 52(3), 1015-1020 CODEN: HTCYAM; ISSN: 0385-5414
PUBLISHER:	Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE:	Journal
LANGUAGE:	English

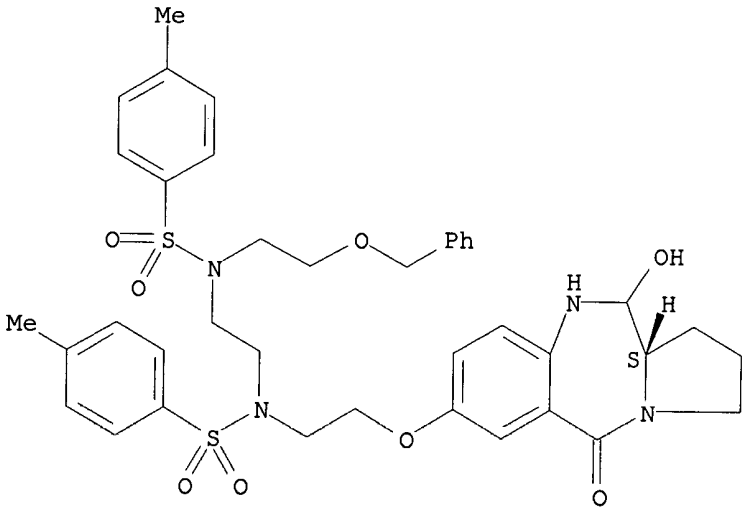
AB A synthetic procedure is described for conjugating polyaminoalkyl groups to the pyrrolo[2,1-c][1,4]benzodiazepine pharmacophore in order to alter its characteristic DNA sequence binding preference. To this end SNAr reactions of 2-nitro-5-fluorobenzoate esters with different polyaminoalkyl side chains were examd. and incorporated in the synthetic scheme.

IT **271253-12-4P 271253-14-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of polyaminoalkyl-substituted pyrrolo[2,1-c][1,4]benzodiazepines)

RN 271253-12-4 CAPLUS

CN Benzenesulfonamide, N-[2-[[(11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-7-yl]oxy]ethyl]-4-methyl-N-[2-[[(4-methylphenyl)sulfonyl][2-(phenylmethoxy)ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

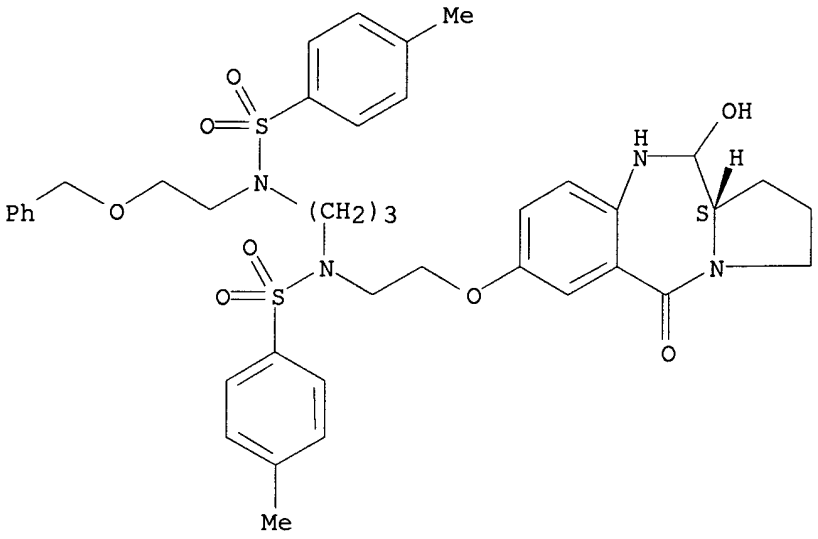
Absolute stereochemistry.



RN 271253-14-6 CAPLUS

CN Benzenesulfonamide, N-[2-[[(11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-7-yl]oxy]ethyl]-4-methyl-N-[3-[[(4-methylphenyl)sulfonyl][2-(phenylmethoxy)ethyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:161285 CAPLUS
DOCUMENT NUMBER: 132:207852
TITLE: Solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivatives for drug screening
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012509	A2	20000309	WO 1999-GB2839	19990827
WO 2000012509	A3	20000706		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9955262	A1	20000321	AU 1999-55262	19990827
EP 1107970	A2	20010620	EP 1999-941767	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525286	T2	20020813	JP 2000-571055	19990827

PRIORITY APPLN. INFO.: GB 1998-18732 A 19980827
WO 1999-GB2839 W 19990827
OTHER SOURCE(S): MARPAT 132:207852

09763813

GI

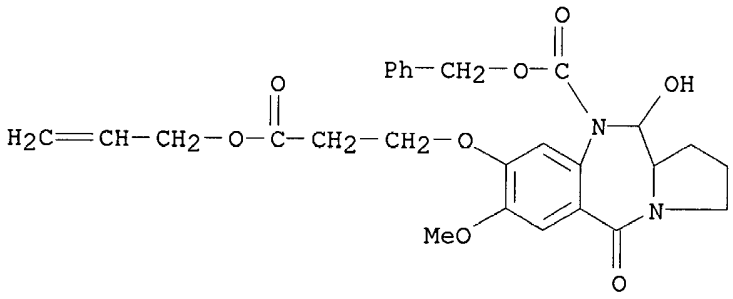
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I are prepd. [wherein: R = (un)substituted alk(en/yn)yl, aralkyl, aryl, or heteroat. analogs; R2 and R3 = H, R, OH, OR, O, :CHR, :CH2, CH2CO2R, CH2CO2H, CH2SO2R, OSO2R, CO2R, COR, and cyano; optionally double bond in ring; R6, R7, R8, and R9 = H, R, OH, OR, halo, NO2, amino, Me3Sn; or R7R8 = O(CH2)1-2O; R11 = H or R; Q = S, O, or NH; L = linking group or bond; Sup = solid support; or where 1 or more of R2, R3, R6, R7 and R8 = independently = H-(T)n-X-Y-A- where: X = CO, NH, S or O; T = combinatorial unit; Y = divalent group such that HY = R; A = O, S, NH, or bond; and n = pos. integer]. The compds. are intermediates for pyrrolobenzodiazepine derivs. II, which are claimed as being potentially useful for treatment of bacterial, parasitic, viral, and gene-based diseases. For example, the supported chloroformate ester III underwent (1) elaboration with 4,5-dimethoxyanthranilic acid, (2) amidation with 2-pyrrolidinemethanol, and (3) oxidative cyclization using SO3.pyridine and DMSO, to give the invention compd. IV. Photochem. cleavage of IV gave the corresponding aminal, which was dehydrated in situ to give the corresponding compd. V. The cleavage product showed cytotoxicity against human leukemia cells which was identical to that of authentic samples of V. Another compd. I was derivatized at a sidechain using 3 amino acids in 3 chain positions to give a 27-member combinatorial library.

IT **260417-30-9DP**, resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; solid-phase prepn. and combinatorial libraries of pyrrolobenzodiazepine derivs. for drug screening)

RN 260417-30-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, phenylmethyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:161284 CAPLUS

DOCUMENT NUMBER: 132:207851

TITLE: Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents

INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson

PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK

SOURCE: PCT Int. Appl., 258 pp.

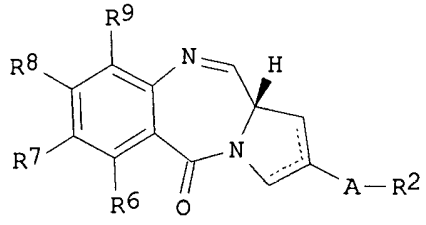
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012508	A2	20000309	WO 1999-GB2838	19990827
WO 2000012508	A3	20000921		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9956351	A1	20000321	AU 1999-56351	19990827
EP 1109812	A2	20010627	EP 1999-943066	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1193270	A2	20020403	EP 2001-129700	19990827
EP 1193270	A3	20020417		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525285	T2	20020813	JP 2000-571054	19990827

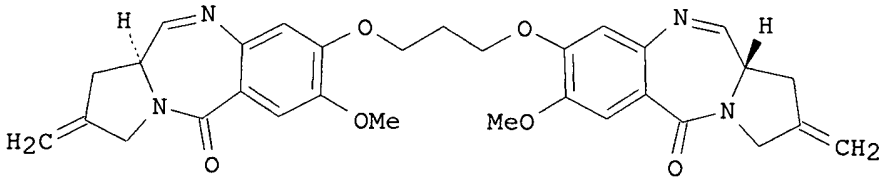
PRIORITY APPLN. INFO.:
GB 1998-18733 A 19980827
GB 1999-1929 A 19990128
EP 1999-943066 A3 19990827
WO 1999-GB2838 W 19990827

OTHER SOURCE(S): MARPAT 132:207851

GI



I



II

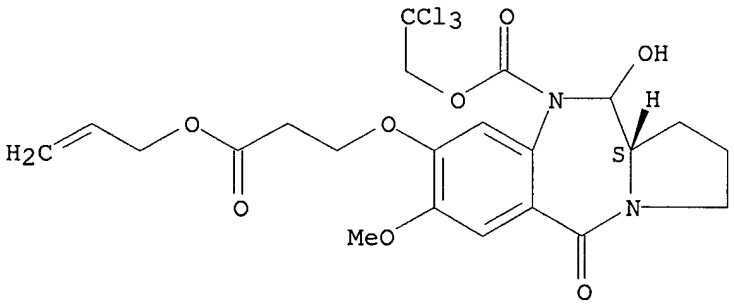
AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein A = CH2 or a single bond; R = (un)substituted (ar)alkyl, (ar)alkenyl, or (ar)alkynyl; R2 = R, OH, OR, CO2H, CO2R, COH, COR, SO2R, CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NHR, NO2, SnMe3; or the compd. is a dimer with each monomer being the same or different and being of formula I

and the R8 groups of the monomers form a -X-R'-X- bridge, where R' is an alkylene chain which may contain .gtoreq. 1 heteroatoms and/or arom. rings and/or carbon-carbon double or triple bonds, and each X = independently O, S, or N] were prepd. for the treatment of gene-based diseases, e.g. neoplastic diseases and Alzheimer's disease, and also bacterial, parasitic, and viral infections. For example, II was synthesized in a 6-step sequence. 1',3'-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (prepn. given) was bisamidated with (2S)-2-(tert-butyldimethylsilyloxymethyl)-4-methylenepyrrolidine (74%). TBAF-mediated cleavage of the silyl protecting groups (94%), followed by redn. of the nitro groups by NH2NH2 in the presence of Raney Ni (63%) and N-acylation with allyl chloroformate (50%), gave the protected diamine. Ring closure was accomplished under Swern oxidn. conditions, (COCl)2-DMSO and TEA, (32%). Finally, the imine was formed from the carbinolamine by N-deprotection using Pd(PPh3)4 and elimination of H2O (77%). Both large scale in vitro cytotoxicity cell screens and and in vivo hollow fiber and human tumor xenograft assays were performed on selected compds. of the invention. For instance, II exhibited potent and selective cytotoxicity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75, and the melanoma cell lines MALME-3M (very potent, 0.08 .mu.M) and UACC-62 (very potent, 0.07 .mu.M). In human xenograft studies against five types of tumors, II demonstrated anticancer activity with mixed toxicity results. In addn., II was shown to be the most potent DNA-stabilizing agent known to date according to a DNA helix melting temp. assay. The IC50 value for II in the A2780 human ovarian carcinoma cell line was only 23 pM, a 320-fold increase in cytotoxicity compared to the known antitumor agent DSB-120 (IC50 = 5.2 nM). Remarkably, II was also almost 9000-fold more potent in the cisplatin-resistant A2780cisR cell line (IC50 = 24 pM) than DSB-120 (IC50 = 0.21 mM), suggesting that II may have potential in the treatment of cisplatin-refractory disease.

IT **260420-49-3P 260420-55-1P 260420-61-9P**
260420-67-5P 260420-74-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 260420-49-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

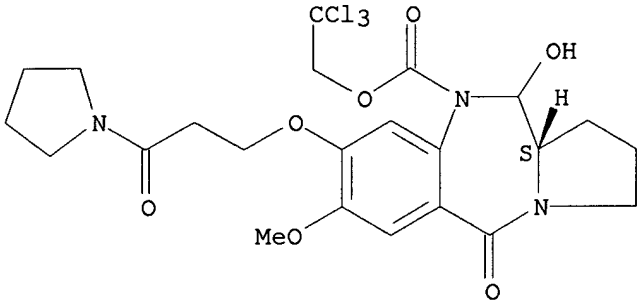
Absolute stereochemistry.



RN 260420-55-1 CAPLUS

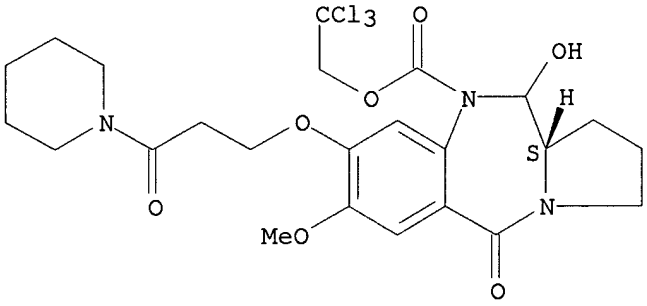
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(1-pyrrolidinyl)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



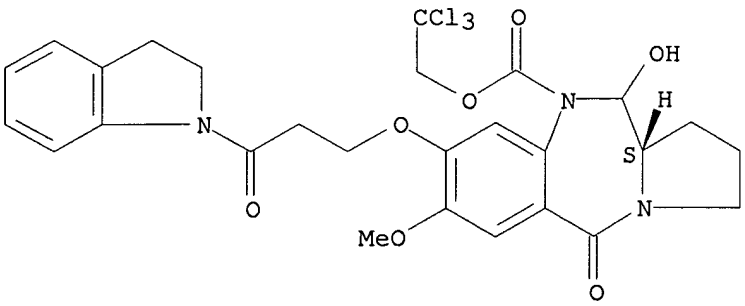
RN 260420-61-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(1-piperidinyl)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

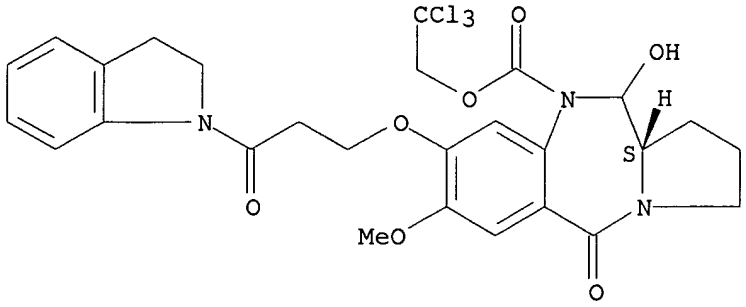
Absolute stereochemistry.



RN 260420-67-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-(2,3-dihydro-1H-indol-1-yl)-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

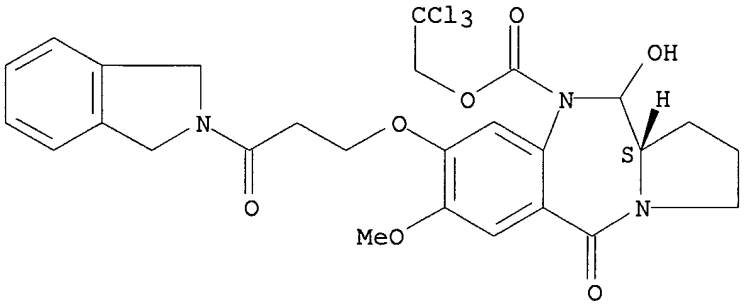
Absolute stereochemistry.





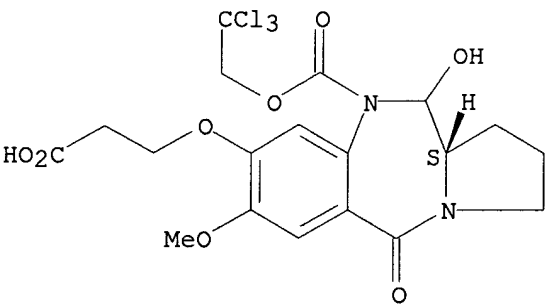
RN 260420-74-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-(1,3-dihydro-2H-isoindol-2-yl)-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

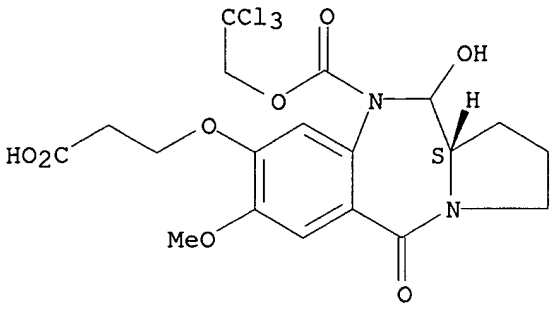
Absolute stereochemistry.



IT **260417-65-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(target compd.; prepn. of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)
RN 260417-65-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(2,2,2-trichloroethyl) ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:161282 CAPLUS
DOCUMENT NUMBER: 132:208134
TITLE: Preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012506	A2	20000309	WO 1999-GB2836	19990827
WO 2000012506	A3	20000629		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9955260	A1	20000321	AU 1999-55260	19990827
EP 1107969	A2	20010620	EP 1999-941765	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525283	T2	20020813	JP 2000-571052	19990827

PRIORITY APPLN. INFO.: GB 1998-18730 A 19980827
WO 1999-GB2836 W 19990827

OTHER SOURCE(S): MARPAT 132:208134
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

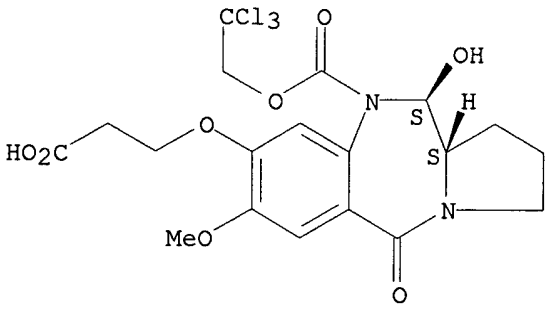
AB Benzodiazepines I [X = CO2H, NH2 or protected amino, SH, OH; A = O, S, NH, or a single bond; R2, R3 = H, R, OH, OR, :O, :CHR, :CH2, CH2CO2R, CH2CO2H, CH2SO2R, OSO2R, CO2R, COR, CN, where R = alkyl, alkenyl, alkynyl, aralkyl,

(un)substituted aryl; there is optionally a double bond between C1 and C2 or C2 and C3; R6, R7, R9 = H, R, OH, OR, halo, nitro, amino, Me3Sn; R11 = H or R; Q = S, O or NH; R10 is a nitrogen-protecting group; Y is a divalent group such that HY = R] were prepd. and incorporated into peptides for use as pharmaceuticals. Thus, pyrrolo[2,1-c][1,4]benzodiazepine deriv. II (Fmoc = fluorenylmethoxycarbonyl) was prepd. and applied to the synthesis of a 27-member glycine/valine/phenylalanine tripeptide library which was screened for inhibition of leukemia cells.

IT **256949-59-4P 260449-60-3P 260449-61-4P**
260449-63-6P 260449-64-7P 260449-66-9P
260449-67-0P 260450-78-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of peptidyl pyrrolobenzodiazepines as pharmaceuticals)

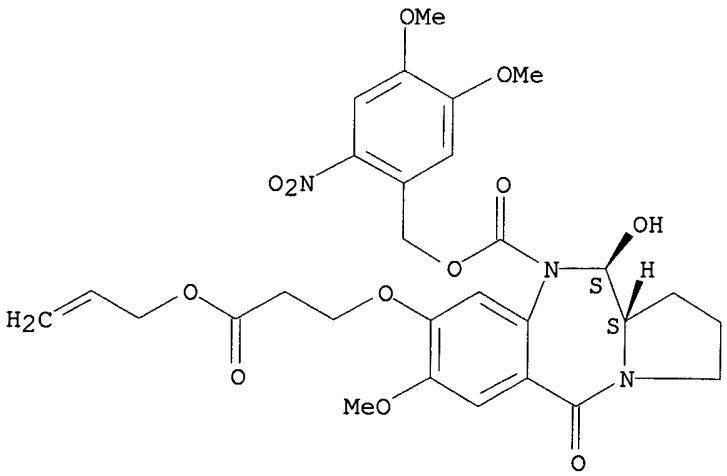
RN 256949-59-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(2,2,2-trichloroethyl) ester, (11S,11aS)- (9CI) (CA INDEX NAME)

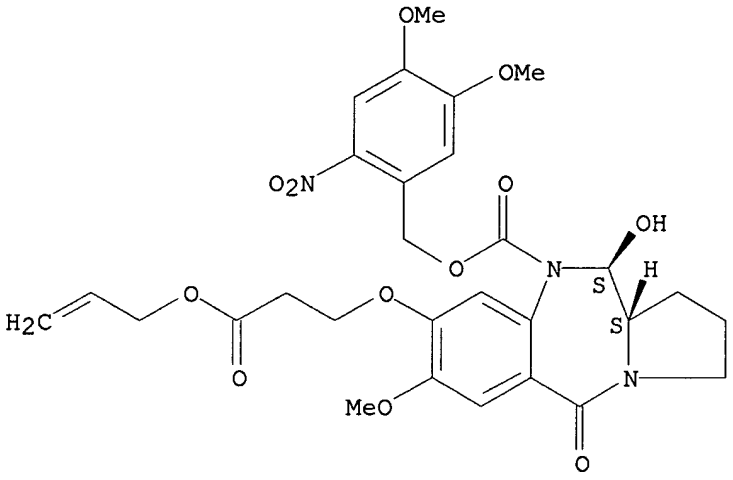
Absolute stereochemistry. Rotation (+).



RN 260449-60-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

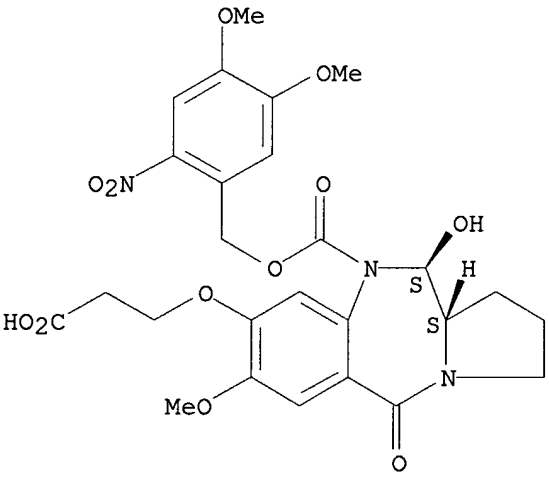
Relative stereochemistry.





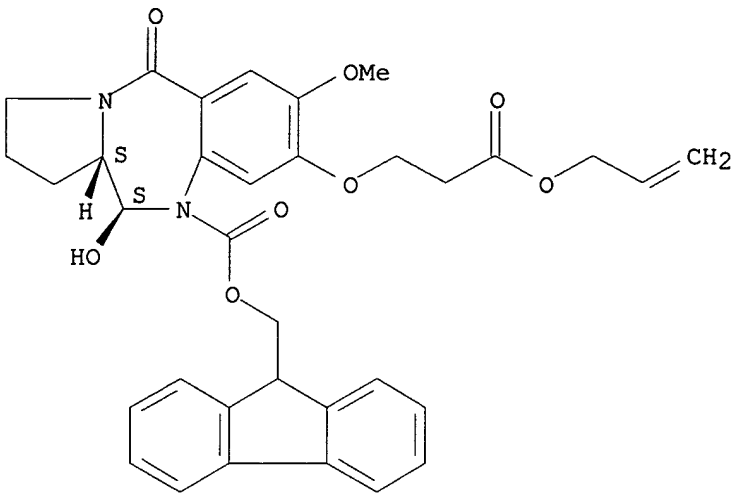
RN 260449-61-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



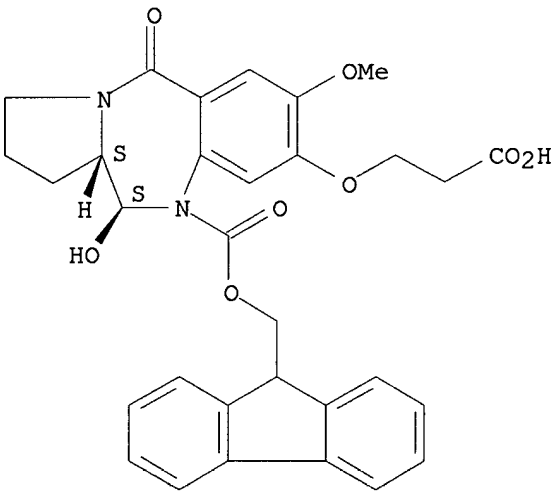
RN 260449-63-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 9H-fluoren-9-ylmethyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



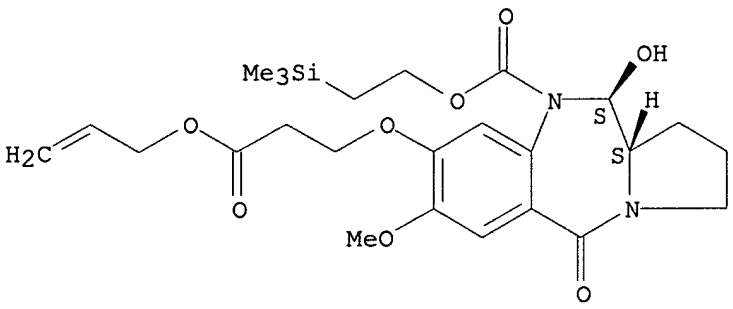
RN 260449-64-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(9H-fluoren-9-ylmethyl) ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



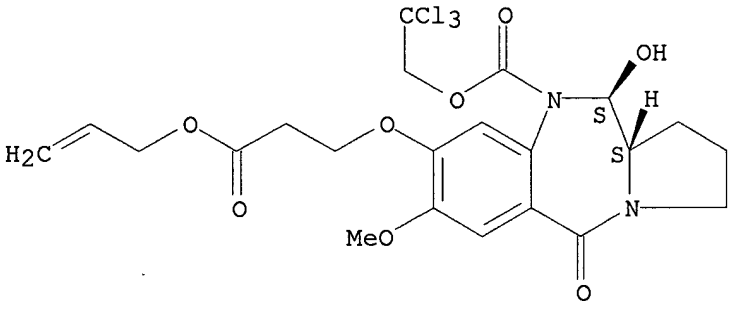
RN 260449-66-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 2-(trimethylsilyl)ethyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



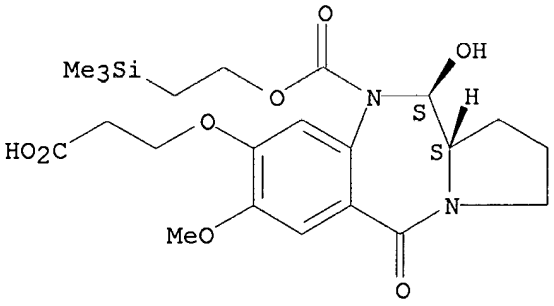
RN 260449-67-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 260450-78-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-[2-(trimethylsilyl)ethyl] ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:758546 CAPLUS
DOCUMENT NUMBER: 132:137361
TITLE: Synthesis, in Vitro Antiproliferative Activity, and DNA-Binding Properties of Hybrid Molecules Containing

09763813

Pyrrolo[2,1-c][1,4]benzodiazepine and Minor-Groove-Binding Oligopyrrole Carriers

AUTHOR(S): Baraldi, Pier Giovanni; Balboni, Gianfranco; Cacciari, Barbara; Guiotto, Andrea; Manfredini, Stefano; Romagnoli, Romeo; Spalluto, Giampiero; Thurston, David E.; Howard, Philip W.; Bianchi, Nicoletta; Rutigliano, Cristina; Mischiati, Carlo; Gambari, Roberto

CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche e Dipartimento di Biochimica e Biologia Molecolare, Universita di Ferrara, Ferrara, 44100, Italy

SOURCE: Journal of Medicinal Chemistry (1999), 42(25), 5131-5141
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 132:137361

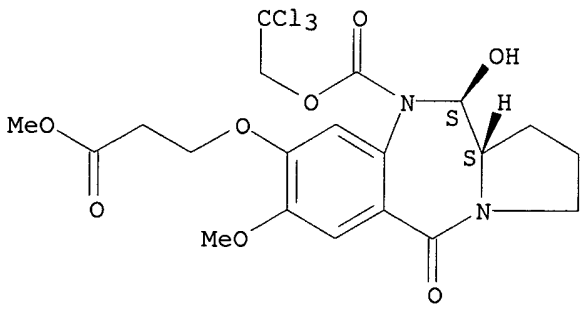
AB The synthesis, biol. activity, and DNA-binding properties of a series of four pyrrolo[2,1-c][1,4]benzodiazepine (PBD) hybrids contg. polypyrrole side chains are described and structure-activity relationships examd. To investigate sequence selectivity and stability of drug/DNA complexes, DNase I footprinting and arrested polymerase chain reaction (PCR) were performed on human c-myc oncogene, estrogen receptor gene, and human immunodeficiency virus type 1 long terminal repeat (HIV-1 LTR) gene sequences. The antiproliferative activity of the hybrids was tested in vitro on human myeloid leukemia K562 and T-lymphoid Jurkat cell lines and compared to antiproliferative effects of the natural product distamycin A 1, its tetrapyrrole homolog, DC 81, and a PBD ester. The new hybrids exhibit different DNA-binding activity with respect to both distamycin A 1 and the parent PBD. In addn., a direct relationship was found between the no. of pyrrole rings present in the hybrids and the stability of drug/DNA complexes. With respect to antiproliferative effects, it was found that the increase in the length of the polypyrrole backbone leads to an increase of in vitro antiproliferative effects, i.e., the hybrid with 4 pyrroles is more active than the other ones both against K562 and Jurkat cell lines.

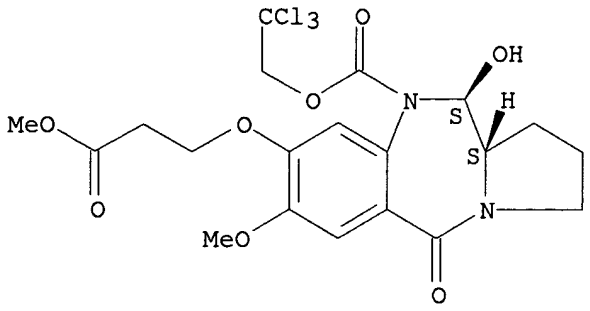
IT **219562-65-9P 256949-59-4P 256949-63-0P**
256949-64-1P 256949-65-2P 256949-66-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn., antiproliferative activity, and DNA-binding pyrrolobenzodiazepines contg. oligopyrrole carriers)

RN 219562-65-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(3-methoxy-3-oxopropoxy)-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

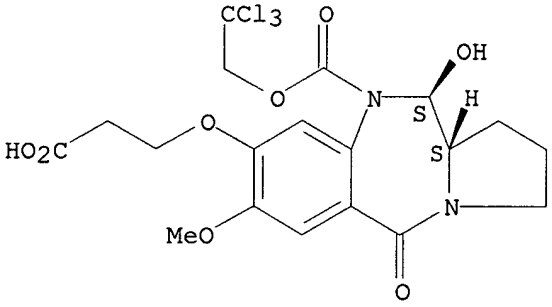
Absolute stereochemistry. Rotation (+).





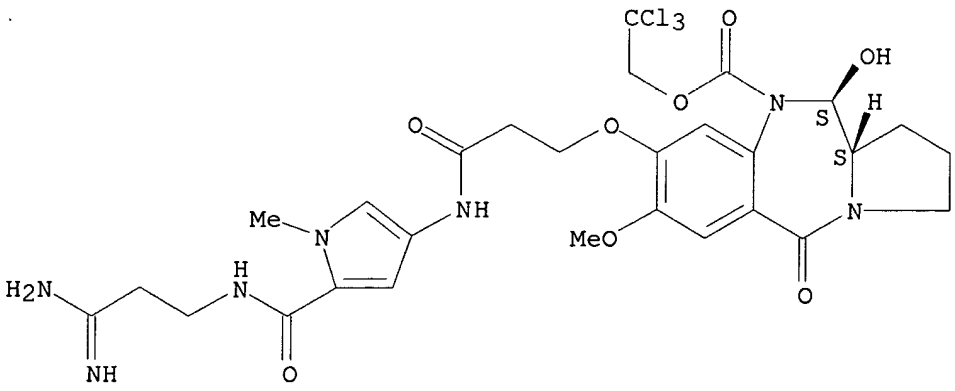
RN 256949-59-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(2,2,2-trichloroethyl) ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 256949-63-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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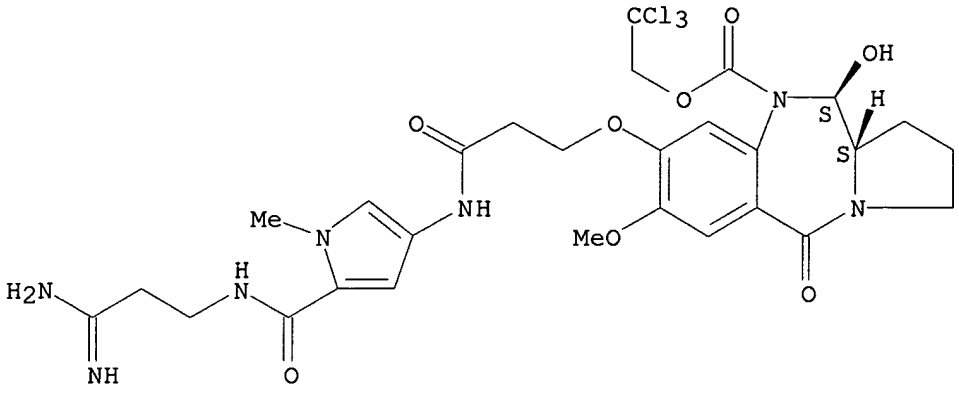
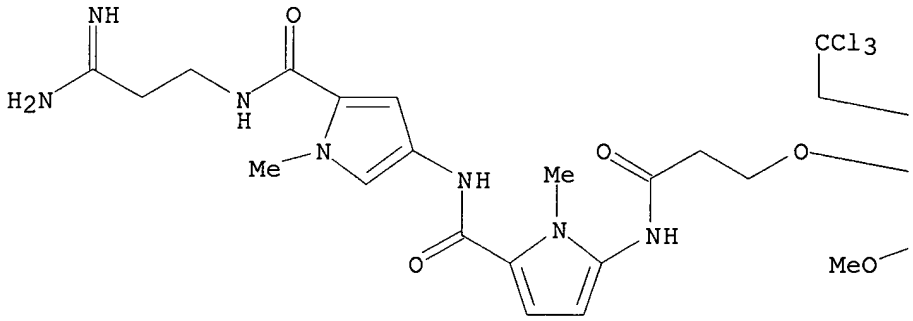


● HCl

RN 256949-64-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

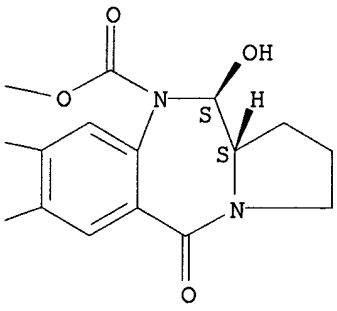
Absolute stereochemistry.

PAGE 1-A



● HCl

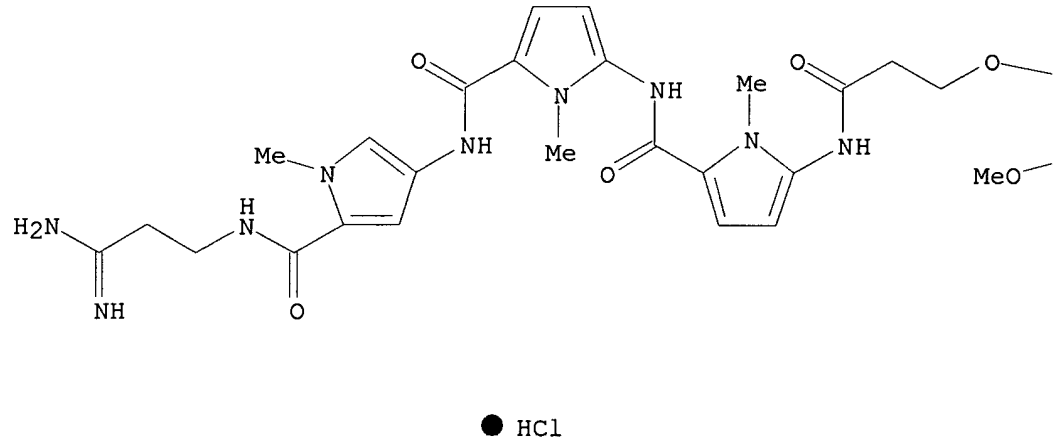
PAGE 1-B



RN 256949-65-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

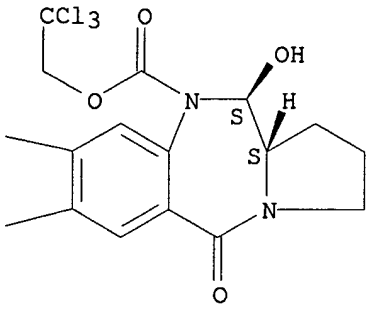
Absolute stereochemistry.

PAGE 1-A



● HCl

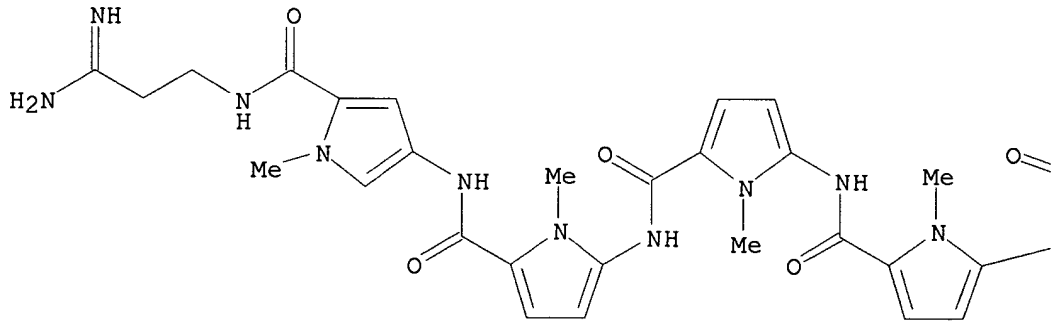
PAGE 1-B



RN 256949-66-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

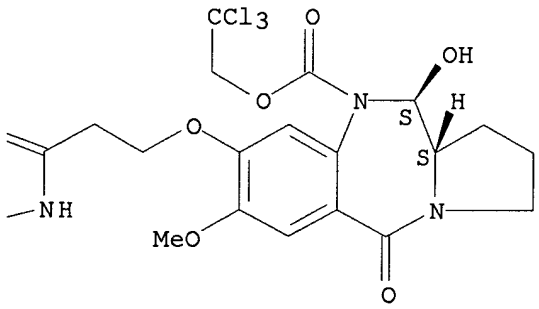
Absolute stereochemistry.

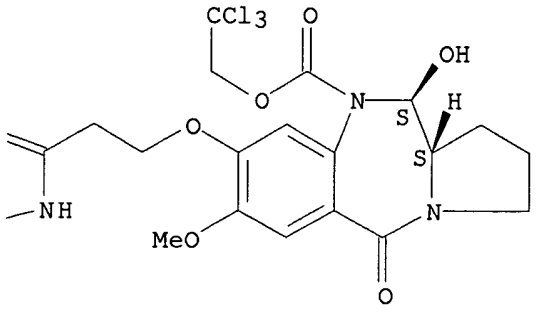
PAGE 1-A



● HCl

PAGE 1-B





REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:760824 CAPLUS
DOCUMENT NUMBER: 130:95405

TITLE: Design, synthesis and biological activity of a pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid

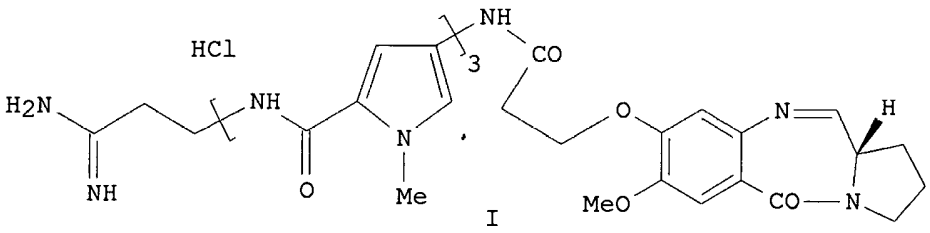
AUTHOR(S): Baraldi, Pier Giovanni; Cacciari, Barbara; Guiotto, Andrea; Leoni, Alberto; Romagnoli, Romeo; Spalluto, Giampiero; Mongelli, Nicola; Howard, Philip W.; Thurston, David E.; Bianchi, Nicoletta; Gambari, Roberto

CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche, Universita di Ferrara, Ferrara, 44100, Italy

SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(21), 3019-3024
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:95405

GI



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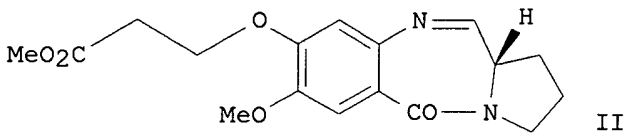


II

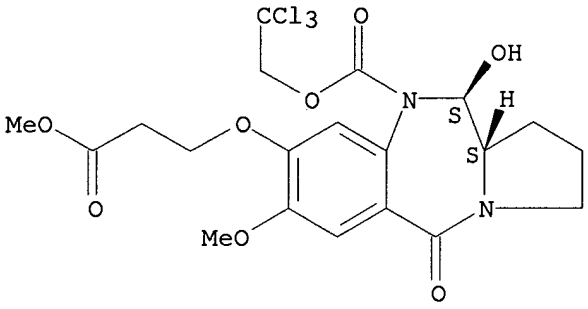
AB The authors report the synthesis of a new hybrid (I) which is a combination of the naturally occurring antitumor agent distamycin A and

the pyrrolo[2,1-c][1,4]benzodiazepine (II), related to naturally occurring anthramycin. The antitumor activity of the hybrid I was tested in vitro and compared to the natural product distamycin A and the PBD II.

IT **219562-65-9P 219562-76-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis and biol. activity of a pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid)

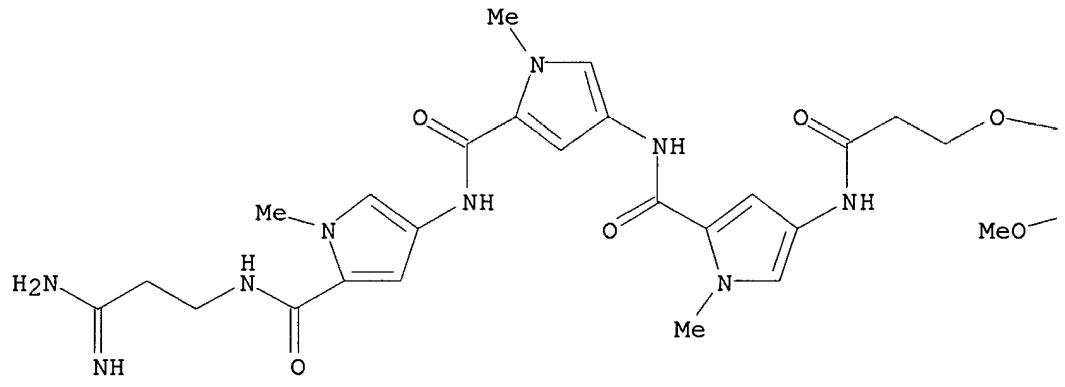
RN 219562-65-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(3-methoxy-3-oxopropoxy)-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

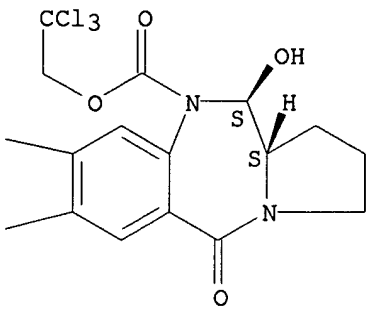


RN 219562-76-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[5-[[[5-[[[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

09763813

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1613SXW

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 09	JAPIO to be reloaded August 25, 2002
NEWS 20	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 21	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 22	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 23	Aug 26	Sequence searching in REGISTRY enhanced

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:59:05 ON 03 SEP 2002

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 10:59:13 ON 03 SEP 2002

STRUCTURE FILE UPDATES: 2 SEP 2002 HIGHEST RN 446017-05-6
DICTIONARY FILE UPDATES: 2 SEP 2002 HIGHEST RN 446017-05-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

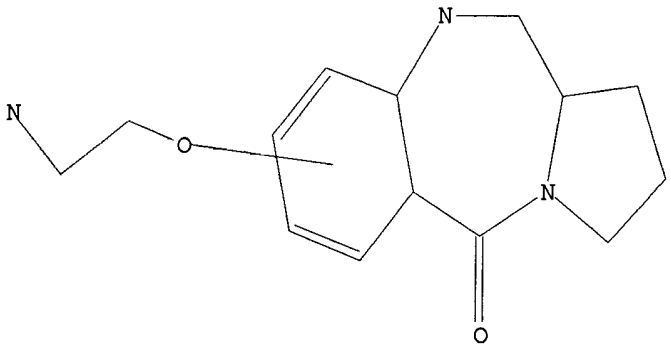
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09763813b.str

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss sam
SAMPLE SEARCH INITIATED 10:59:58 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 166 TO ITERATE

09763813

100.0% PROCESSED 166 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 2547 TO 4093
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 11:00:03 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 3424 TO ITERATE

100.0% PROCESSED 3424 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.02

L3 2 SEA SSS FUL L1

=> fil cap;us
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 140.66 140.87

FILE 'CAPLUS' ENTERED AT 11:00:09 ON 03 SEP 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 3 Sep 2002 VOL 137 ISS 10
FILE LAST UPDATED: 2 Sep 2002 (20020902/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

US IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> fil cap;us
COST IN U.S. DOLLARS SINCE FILE TOTAL

09763813

	ENTRY	SESSION
FULL ESTIMATED COST	0.40	141.27

FILE 'CAPLUS' ENTERED AT 11:00:13 ON 03 SEP 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 3 Sep 2002 VOL 137 ISS 10
FILE LAST UPDATED: 2 Sep 2002 (20020902/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

US IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system. For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.40	141.67

FILE 'CAPLUS' ENTERED AT 11:00:16 ON 03 SEP 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 3 Sep 2002 VOL 137 ISS 10
FILE LAST UPDATED: 2 Sep 2002 (20020902/ED)

09763813

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l3 full
L4 1 L3

=> d l4

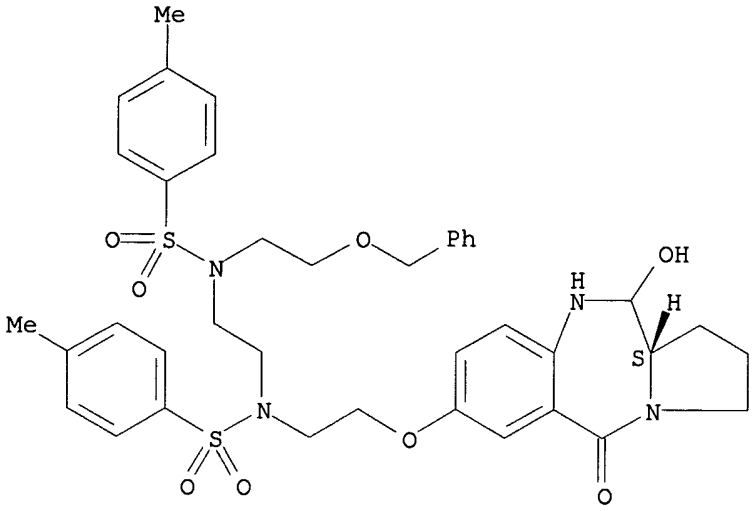
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AN 2000:244166 CAPLUS
DN 133:4639
TI Synthesis of polyaminoalkyl substituted conjugates of pyrrolo[2,1-c][1,4]benzodiazepine involving SNAr reaction of 2-nitro-5-fluorobenzoate precursors
AU Matsumoto, Kiyoshi; Iida, Hirokazu; Lown, J. William
CS Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, 606-8501, Japan
SO Heterocycles (2000), 52(3), 1015-1020
CODEN: HTCYAM; ISSN: 0385-5414
PB Japan Institute of Heterocyclic Chemistry
DT Journal
LA English
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l4 ibib abs hitstr

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:244166 CAPLUS
DOCUMENT NUMBER: 133:4639
TITLE: Synthesis of polyaminoalkyl substituted conjugates of pyrrolo[2,1-c][1,4]benzodiazepine involving SNAr reaction of 2-nitro-5-fluorobenzoate precursors
AUTHOR(S): Matsumoto, Kiyoshi; Iida, Hirokazu; Lown, J. William
CORPORATE SOURCE: Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, 606-8501, Japan
SOURCE: Heterocycles (2000), 52(3), 1015-1020
CODEN: HTCYAM; ISSN: 0385-5414
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A synthetic procedure is described for conjugating polyaminoalkyl groups to the pyrrolo[2,1-c][1,4]benzodiazepine pharmacophore in order to alter its characteristic DNA sequence binding preference. To this end SNAr reactions of 2-nitro-5-fluorobenzoate esters with different polyaminoalkyl side chains were examd. and incorporated in the synthetic scheme.
IT **271253-12-4P 271253-14-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of polyaminoalkyl-substituted pyrrolo[2,1-c][1,4]benzodiazepines)
RN 271253-12-4 CAPLUS
CN Benzenesulfonamide, N-[2-[[(11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-7-yl]oxy]ethyl]-4-methyl-N-[2-[[(4-methylphenyl)sulfonyl][2-(phenylmethoxy)ethyl]amino]ethyl]- (9CI) (CA

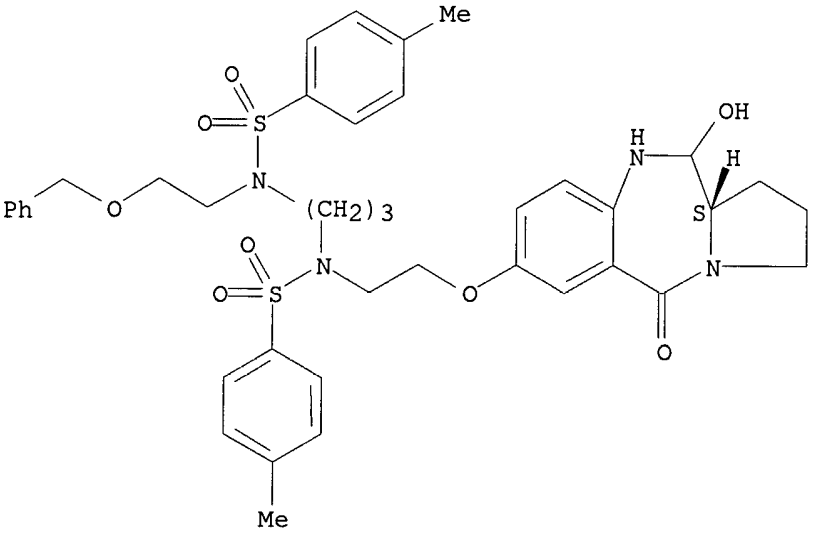
INDEX NAME)

Absolute stereochemistry.



RN 271253-14-6 CAPLUS
CN Benzenesulfonamide, N-[2-[[(11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-7-yl]oxy]ethyl]-4-methyl-N-[3-[[(4-methylphenyl)sulfonyl][2-(phenylmethoxy)ethyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT